PRINCIPAL
REGIONAL TECHNICAL COLLEGE
PORT ROAD,
LETTERKENNY.

B17/6 133 £10.0

This book is to be returned on or before
the last date stamped below.

A

A/547
Raphael, R.A.
Taylor, E.C.
Wynberg, H.
Advances in Organic chemistry.
Methods and results.
Volume 2.

A/547 Vol. II

Donagh O'Malley,
R. T. C.
Letterkenny

B

Advances in Organic Chemistry

Methods and Results

VOLUME II

Advisory Board

D. H. R. BARTON
Imperial College of Science and Technology, London, England
K. W. BENTLEY
University of Aberdeen, Scotland
A. J. BIRCH
University of Manchester, England
J. W. COOK
University of Exeter, England
CARL DJERASSI
Stanford University, California
A. ESCHENMOSER
Eidg. Technische Hochschule, Zürich, Switzerland
R. GREWE
Universität Kiel, Germany
R. HUISGEN
Ludwig-Maximilians-Universität, Munich, Germany
E. C. KOOYMAN
Rijksuniversiteit, Leiden, The Netherlands
E. LEDERER
Faculté des Sciences, Paris, France
G. OURISSON
Université de Strasbourg, France
A. QUILICO
Instituto di Chimica Generale del Politecnico, Milan, Italy
S. STÄLLBERG-STENHAGEN
University of Gothenburg, Sweden
G. STORK
Columbia University, New York
SIR ALEXANDER TODD
University Chemical Laboratory, Cambridge, England
M. VISCONTINI
University of Zürich, Switzerland
A. WEISSBERGER
Eastman Kodak Company, Rochester, New York
K. WIESNER
University of New Brunswick, Fredericton, Canada
F. Y. WISELOGLE
Squibb Institute for Medical Research, New Brunswick, New Jersey
R. B. WOODWARD
Harvard University, Cambridge, Massachusetts

Advances in Organic Chemistry

Methods and Results

VOLUME II

Donagh O'Malley
Regional
Letterkenny
WITHDRAWN

Editors

RALPH A. RAPHAEL, *The University, Glasgow, Scotland*
EDWARD C. TAYLOR, *Princeton University, Princeton, New Jersey*
HANS WYNBERG, *Rijksuniversiteit, Leiden, The Netherlands*

1960

Interscience Publishers, Inc., New York
Interscience Publishers Ltd., London

Copyright © 1960 by Interscience Publishers, Inc.
All rights reserved
Library of Congress Catalog Card Number 59-13036

A 1547

Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, New York
For Great Britain and Northern Ireland:
Interscience Publishers Ltd., 88/90 Chancery Lane, London W. C. 2

PRINTED IN THE UNITED STATES OF AMERICA

Contributors to Volume II

J. F. Arens
Organisch Chemisch Laboratorium der Rijksuniversiteit, Groningen, The Netherlands

Harold Conroy
Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut

Niels Elming
Research Division, A/S Pharmacia, Copenhagen-Vanløse, Denmark

C. H. Eugster
Chemisches Institut der Universität, Zürich, Switzerland

L. M. Jackman
Department of Chemistry, Imperial College of Science and Technology, London, England

R. N. Lacey
Development Department, The Distillers Company Ltd. (Chemical Division), Hull, England (present address: *BP Research Centre, Chemicals Division, The British Petroleum Company Ltd., Sunbury-on-Thames, England*)

Paul de Mayo
Department of Chemistry, The University of Western Ontario, London, Ontario, Canada

H. Normant
Laboratoire de Synthèse Organique, Faculté des Sciences, Paris, France

Digitized by the Internet Archive
in 2026

https://archive.org/details/lccn_59013036_2

Contents

Alkenylmagnesium Halides
By H. Normant 1

Dialkoxydihydrofurans and Diacyloxydihydrofurans as Synthetic Intermediates
By Niels Elming 67

Ethynyl Ethers and Thioethers as Synthetic Intermediates
By J. F. Arens 117

Ketene in Organic Synthesis
By R. N. Lacey 213

Nuclear Magnetic Resonance in Organic Structural Elucidation
By Harold Conroy 265

Hydrogenation-Dehydrogenation Reactions
By L. M. Jackman 329

Ultraviolet Photochemistry of Simple Unsaturated Systems
By Paul de Mayo 367

The Chemistry of Muscarine
By C. H. Eugster 427

Author Index 457

Subject Index 484

Cumulative Index, Volumes I–II 504

ALKENYLMAGNESIUM HALIDES

By H. NORMANT,* *University of Paris, France*

CONTENTS

I. Introduction 1
A. Preparation of Alkenylmagnesium Halides 3
B. Nature of the Alkenyl Halide 4
C. Nature of the Magnesium 4
D. Influence of Temperature 5
E. Nature of the Solvent 5
F. Role of the Solvent 6
G. Yields and Secondary Reactions 7
II. Uses of Alkenylmagnesium Halides 9
A. Vinyl Derivatives of Group IV Elements 10
B. Vinyl Derivatives of Group V Elements 11
C. Vinyl Derivatives of Mercury and Boron 12
D. Reactions Involving Rupture of the Carbon–Halogen Bond 14
E. Reactions Involving Rupture of the Carbon–Oxygen Bond 17
F. Reactions with Aldehydes and Ketones 20
G. Reactions with Acid Derivatives and Carbon Dioxide 28
H. Reactions with Some Nitrogen-Containing Compounds 35
III. Experimental 37
A. Preparation of Vinylmagnesium Halides 37
B. Vinyl(tri-*n*-butyl)tin 38
C. (±)-Linaloöl 39
D. 3-Vinyl-2-methylcyclohex-2-enone 39
E. Pent-2-en-4-one 40
IV. Tables of Products 41
References 62

I. Introduction

It is only recently that the numerous attempts to prepare Grignard reagents from alkenyl halides have been crowned with success. For a historical survey, see Braude and Timmons (3).

Diarylvinyl halides, RR′C=CHX (R and R′ = aryl), react normally with magnesium in the presence of ether (88); this, however, is not necessarily true of monoarylvinyl halides (R = aryl; R′ = H or

* Translated by R. P. A. Sneeden, The University, Glasgow, Scotland.

alkyl); and alkenyl halides (R = alkyl; R′ = H or alkyl) seldom give Grignard reagents with magnesium in ether solution. As early as 1902, Tiffeneau (84), in describing the preparation of the first alkenylmagnesium halide, β-styrylmagnesium bromide, reported that the reaction was accompanied by a disproportionation reaction resulting in the formation of styrene and PhC≡CMgBr. More recently Gilman and co-workers (22) have successfully prepared β-styrylmagnesium bromide in 90% yield.

Alkenyl halides, RR′C=CHX (I), in which one of the doubly bonded carbon atoms bears a hydrogen atom and the other a halogen atom (R′ = H), react with a metal, M, to give the alkene and a mixture of the alkenyl- and alkynylorganometallic compounds.

$$\mathrm{RR'C{=}CHX} \xrightarrow{M} \begin{cases} \longrightarrow \mathrm{RCH{=}CHM} \ (\mathrm{II}) & (1) \\ \longrightarrow \mathrm{RCH{=}CH_2} + \mathrm{RC{\equiv}CM} \ (\mathrm{III}) & (2) \end{cases}$$

(I)

(M = Na (15,34), Li, Mg)

In the case of purely aliphatic compounds (I; R and R′ = alkyl or H), the formation of the acetylenic compound (reaction 2) predominates.

With sodium it would appear (44) that the only product is the sodioalkyne (III; M = Na). Morton and co-workers (45), however, have been successful in preparing vinylsodium by the direct metalation of ethylene with amylsodium. The application of this method is rather limited since propene and but-1-ene are metalated at the allyl position.

With lithium (3–6) or organolithium compounds (23,24,87a), it would appear that the product in the case of alkenyl halides can be the alkenyllithium, the alkynyllithium, or a mixture. Thus, it has not been possible to prepare vinyllithium from either vinyl chloride or vinyl bromide (24,87b). *cis*-Propenyl bromide, on the other hand, reacts with lithium to give *cis*-propenyl- and propynyllithium in the proportion 5:1. The composition of the lithium derivative was established by an analysis of its condensation products (7).

Alkenyl halides of the type I (R and R′ = alkyl), which cannot give rise to the acetylenic compounds, react with a metal, M, to give the

alkenylorganometallic compound (IV), the dimeric Wurtz product (V), or a mixture of both.

$$RR'C{=}CHX \xrightarrow{M} \begin{cases} \longrightarrow R'R{=}CHM \quad (IV) & (3) \\ \longrightarrow RR'C{=}CHCH{=}CR'R \quad (V) & (4) \end{cases}$$

Isobutenyl bromide reacts with lithium (3) to give up to 36% of the Wurtz product (eq. 4), whereas isobutenyl chloride gives none (8).

The reaction of magnesium with aliphatic alkenyl compounds (I; R and R′ = alkyl or H) is accompanied by many side reactions, and the yield of organomagnesium halide never exceeds 20% (3,35,37). Vinyl bromide and chloride react with activated magnesium to give practically nothing but acetylene. It has been reported (2a) that vinylmagnesium bromide can advantageously be prepared in ether. It must be pointed out, however, that commercial vinyl bromide in the United States contains approximately 20% of ethyl bromide (1b), which can act as a reaction initiator.

To date no satisfactory preparation of cyclohexenylmagnesium chlorides has been achieved, despite the brilliant results obtained by Braude and his collaborators with cyclohexenyllithium compounds.

A. PREPARATION OF ALKENYLMAGNESIUM HALIDES

The important advances in the preparation of alkenylmagnesium halides made by H. Normant (49) in 1953, and later independently by Ramsden (70), meant that these reagents are now as accessible as the usual alkyl- or arylmagnesium halides.

It was shown (49) that in the Grignard reaction, when certain solvents such as tetrahydrofuran (THF) were used in place of ether, alkenyl halides of the type VI, including vinyl bromide and chloride, react to give the expected alkenylmagnesium halide (VII) in excellent yield:

$$\underset{\text{(VI; X = Cl or Br)}}{\overset{|}{C{=}CX}} \xrightarrow{Mg} \underset{\text{(VII; X = Cl or Br)}}{\overset{| \quad |}{C{=}CMgX}}$$

Although this reaction is applicable to aliphatic, alicyclic, or heterocyclic alkenyl halides, only the aliphatic group will be considered here.

B. NATURE OF THE ALKENYL HALIDE

In all the cases examined the bromo compounds reacted rapidly and smoothly (for preparation, see ref. 61). The reaction has been extended to dibromides prepared from the corresponding enynes.

$$RCH{=}C(R')C{\equiv}CH \xrightarrow{2HBr} RCHBrC(R'){=}CBrCH_3$$

In ether magnesium reacts selectively with the allylic bromine, and the subsequent condensation product can be used in THF solution to prepare the vinylmagnesium halide (25a). With chloro compounds, however, only vinyl chloride gives high yields of the organometallic compound. Other homologs examined, both cyclic and acyclic, proved to be inert (70b). This is unexpected in view of the reactivity of chlorobenzene and other aryl chlorides toward magnesium in THF (49,61,70a). Thus, in the case of chlorocycloalkenes, the method of Braude is of great significance.

A comparative study of the ease of formation of the organometallic systems shown below (M = Li, MgBr) has recently been reported (42a).

(X = Cl, Br; M = Li, MgBr)

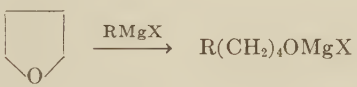
Based on the yield of the halide as well as the yield of the resulting organometallic compound, the following conclusions were reached: (*a*) in the cyclopentenyl series ($n = 3$), the use of magnesium is advantageous; (*b*) in the cyclohexenyl series ($n = 4$), the two organometallic compounds appear to be formed in equivalent yields; and (*c*) in the cyclooctenyl series ($n = 6$), it is preferable to use the lithium derivative.

C. NATURE OF THE MAGNESIUM

Commercial magnesium is satisfactory in most instances; however, as in all Grignard reactions, a metal of high purity is indicated in order to avoid any secondary reactions (32). Pure magnesium turnings, approximately 2 × 3 mm. in size, are recommended.

D. INFLUENCE OF TEMPERATURE

Since the solvents used are all ethers and organomagnesium halides react with ether at elevated temperatures, some control of the reaction temperature is indicated. It is advisable that, once the reaction has started, the rate of addition of halide in the appropriate solvent should be so controlled as to maintain the reaction temperature in the region 40–50° and never at the reflux point. Under such conditions the side reactions referred to earlier, i.e., disproportionation and coupling, will not take place. Furthermore, organomagnesium halides, even complex ones, do not react appreciably with THF at ordinary temperatures (63). It is only at elevated temperatures (190–200°) that THF, being a 1,4-epoxide, undergoes reaction with organomagnesium compounds to give primary alcohols containing four additional carbon atoms (49):



$$\xrightarrow{\text{RMgX}} \text{R(CH}_2\text{)}_4\text{OMgX}$$

E. NATURE OF THE SOLVENT

When the reaction is carried out in cyclic ethers such as THF, 2-methyl-THF, tetrahydropyran, etc., or diethers of di- and polyethylene glycols ($ROCH_2CH_2(OCH_2CH_2)_nOR$; $n \geq 1$), excellent yields of the organomagnesium halide are obtained. That the products are pure alkenylmagnesium halides is proven by the spectral analysis (infrared) of subsequent reaction products.

When cyclic ethers are used, the complex formed between the alkenylmagnesium halide and the solvent is liable to crystallize from the cool solution (vinylmagnesium chloride being the exception). It is therefore advisable, where inverse additions are envisaged, to use an appropriately designed flask. With the second type of solvent most solutions of the organometallic compounds showed no tendency to crystallize, even at 0°. In either case the formation of the Grignard reagent is indicated by a complete disappearance of the metal and the formation of a clear brown solution.

The relative proportions of solvent and alkenyl halide have little or no influence on the final yields. In general, 50–60 ml. of solvent is used for 0.1 mole of halide, though higher dilutions are recommended for styryl bromides.

Table I illustrates the percentage yields obtained in different solvents. The availability of solvents with widely differing boiling points means that a solvent may be chosen such that the final reaction product can readily be isolated by distillation. Once prepared, the alkenylmagnesium halide, and likewise the substance with which it is to be reacted, may be mixed with or added to a different inert solvent (e.g., ether).

TABLE I

Yields of $CH_3CH{=}CHC(OH)(CH_3)_2$ Obtained from Reaction of Isopropenyl Bromide (0.1 mole), Magnesium (0.1 g.-atom), and Acetone (0.07 mole) in Different Solvents

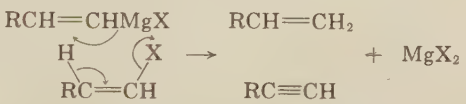
Solvent	Boiling point, °C.	Yield, %
THF	66/760 mm.	75–80
2-Methyl-THF	80/760 mm.	75–80
Tetrahydropyran	87/760 mm.	70–75
$C_2H_5(OCH_2CH_2)_2OC_2H_5$	80/16 mm.	80–85
n-$C_4H_9(OCH_2CH_2)_2OC_4H_9$	132/16 mm.	80

Other solvents or mixtures of solvents can be used (61), but they give poorer yields, and in some cases disproportionation of the alkenylmagnesium halide to the alkynylmagnesium compound may occur. The final choice of solvent will depend on the halide employed and the nature of the ultimate reaction product.

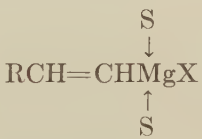
F. ROLE OF THE SOLVENT

The solvent properties of cyclic ethers and ethers of ethylene glycols are already well known and have been employed in many reactions. These properties must doubtless facilitate the interaction of the halide and the magnesium by keeping the metal surface clean. However, they do not account for the fact that chlorobenzene reacts with magnesium whereas 1-chlorocyclohexene does not. The solvents in question, especially tetrahydrofuran, being stronger bases than aliphatic ethers, can form coordination complexes with organometallic compounds and thereby remove these compounds from the metal surface as soon as they are formed. This difference in basicity is demonstrated by the facts that THF will displace diethyl ether from organomagnesium etherates (49) and BF_3 etherate (48) and, as Wiberg has shown (86), is capable of uniting with AlH_3, $LiAlH_4$, $LiBH_4$, etc.

Furthermore, it has been shown that there is a direct relationship between the availability of the lone pair of electrons on the oxygen atom and formation of an organomagnesium compound in that solvent. Thus, in solvents in which the availability of the lone pair of electrons is affected by resonance effects (e.g., furan) or steric effects (e.g., 2,5-dimethyl-THF and 2,2,5,5-tetramethyl-THF), it is not possible to prepare the arylmagnesium halides. This solvation of the Grignard reagent by THF in no way prevents it from undergoing all the normal reactions (contrary to what might be expected from the work of Lewis and Wright (40)). Perhaps it is precisely this basicity of THF which is responsible for the formation of the normal organomagnesium compound. When the solvent is *not* attached to the magnesium and there is a hydrogen atom on the carbon atom α to the halogen-bearing one, the disproportionation reaction can be envisaged as occurring via a cyclic transition state similar to that postulated by Kharasch and Reinmuth (33) for the saturated halides. On the other



hand, when the solvent, S, is firmly attached to the magnesium of the alkenylmagnesium halides, the formation of such a cyclic transition state is prevented and thus disproportionation does not occur.



G. YIELDS AND SECONDARY REACTIONS

The yields obtained in the formation of alkenylmagnesium halides are comparable to those obtained in the formation of the Grignard reagents from alkyl and aryl halides in ether. Analysis by the method described by Gilman and co-workers (21) often gives values of the order of 95% based on the alkenyl halide. The procedure of Job and Reich (27), on the other hand, gives erroneous results owing to the action on THF of the iodine used in the method. Analysis of vinylmagnesium bromide by measuring the ethylene liberated also gives

TABLE II

R	[RLi] $\xrightarrow{CO_2}$ RCOOH: Product obtained	Yield, %	Ref.	[RMgX] $\xrightarrow{CO_2}$ RCOOH: Product obtained	Yield, %	Ref.
CH_2=CH—	Could not be prepared	—	9	CH_2=CHCOOH	47	57
CH_3CH=CH—	CH_3C≡CCOOH	6	7	CH_3CH=CHCOOH	66	57
	$(CH_3CH$=$CH)_2CO$	15				
$(CH_3)_2C$=CH—	$(CH_3)_2C$=CHCOOH	7	3	$(CH_3)_2C$=CHCOOH	50	57
$(CH_3)_2C$=$C(CH_3)$—	$(CH_3)_2C$=$C(CH_3)$COOH	17	9	$(CH_3)_2C$=$C(CH_3)$COOH	29	57
	Product with C_6H_5CHO					
CH_2=$C(CH_3)$—	$C_6H_5CH(OH)C(CH_3)$=CH_2	72	9a	$C_6H_5CH(OH)C(CH_3)$=CH_2	80	39

excellent results; thus Weyenberg (85) reports 95% by this method as against 97% by the method of Gilman.

The alkenylmagnesium halides also give the color reactions of Gilman and Schulze (20).

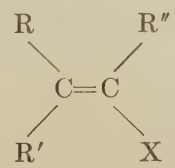
In the preparation of the organomagnesium compounds from arylvinyl halides, such as α- and β-styryl bromide and α-methyl-β-styryl bromide, special precautions are necessary. The concentration of the halide in THF must be decreased and the rate of addition to the magnesium so controlled that the reaction temperature does not exceed 30°. In this way a high yield of the organomagnesium halide is ensured.

The present success associated with the use of THF in place of ether as solvent has led to its being used for the formation of other organometallic compounds (66a,83). Thus, in the case of organolithium compounds, the use of THF results in a more rapid reaction and higher yields (25). However, it must be emphasized that in some cases ether is superior to THF as solvent (as, for example, in the formation of saturated alkylmagnesium halides). In this instance the Wurtz reaction competes with the formation of the Grignard compound, and, in THF, the yield of Wurtz product increases in the order Cl < Br < I (this is also the case with benzylic, allylic, and propargyllic bromides (44a)), and is almost quantitative for iodo compounds.

Table II indicates the percentage yield obtained in the formation of lithium alkenyls and alkenylmagnesium halides as estimated by their subsequent reactions with CO_2.

II. Uses of Alkenylmagnesium Halides

Because of their ease of preparation, the high yields obtained, and their reactivity, alkenylmagnesium halides are of great importance in preparative chemistry. As will be illustrated in the following pages, they have already furnished the means of synthesis for various compounds containing an ethylenic group and in particular the vinyl group. It has been reported that the magnesium derivatives of VIII



(VIII)

react with retention of configuration. This offers many possibilities for stereospecific syntheses (see Section II-G-6).

A. VINYL DERIVATIVES OF GROUP IV ELEMENTS

The present-day knowledge of vinyl derivatives of the elements of groups IV and V is largely due to the studies of Seyferth and co-workers (78-83) at Harvard University in 1956 and of Petrov (69a).

The organometallic compounds of types IX and X can be prepared in excellent yield by the action of the appropriate organometallic compound and vinylmagnesium halide:

$$n(CH_2{=}CH)MgCl + R_{4-n}M^{IV}Cl_n \longrightarrow R_{4-n}M^{IV}(CH{=}CH_2)_n + nMgCl_2$$

(IX; R = alkyl)
(X; R = aryl)

Any other alkenyl halide could be used in place of the vinyl halide in the above reaction (for results see Table IX).

1. Vinylsilanes. The great industrial applications of many silicon compounds had already led to the preparation and study of alkenylsilanes (69,73). However, the introduction of alkenylmagnesium halides in this field engendered significant developments; thus Rosenberg and co-workers (74) used vinylmagnesium chloride for the preparation of several mono- and polyvinylsilanes.

2. Vinyltins. Prior to the studies of Seyferth and Stone (78) only a few isolated examples of this class of compound were known, and they were all monovinyltin compounds. Seyferth and Stone found that compounds of types IX and X (M = Sn; n = 1–3) could be prepared by treating organotin halides with excess vinylmagnesium bromide; this method was used to prepare a variety of compounds, and the yields ranged from 70 to 85%. They do not, however, appear to have studied the systematic replacement of the halogen atom of $R_{4-n}M^{IV}Cl_n$ by the vinyl group. They prepared the vinyltin chlorides of the type XI by the action of stannic chloride on alkylvinyltins:

$$R_{4-n}Sn^{IV}(CH{=}CH_2)_n \xrightarrow{SnCl_4} (CH_2{=}CH)_nSnCl_{4-n}$$

(XI)

Seyferth showed (79) that vinyltin compounds, in contrast to vinylsilanes, do not undergo addition reactions with halogens or protonic

acids (such as the hydrogen halides or organic acids); instead, they lose one or more vinyl groups to give the corresponding organotin halides (or esters) XII and XIII.

$R_2(CH_2{=}CH)SnX$ (XII; X = Cl, Br, I, $CH_3CHBrCOO{-}$) $(CH_2{=}CH)_3SnX$ (XIII; X = I or F)

About this time Rosenberg and co-workers (75) also prepared alkylvinyltin compounds of types IX and X (M = Sn) and tetravinyltin by the action of vinylmagnesium chloride on the appropriate tin chloride in yields ranging from 73 to 89%. Furthermore, they were successful in preparing chlorovinyltin compounds by the controlled reaction of an organotin chloride and vinylmagnesium chloride; the yields, however, were in the order of 50–60%. For a preparative method for vinyltin chlorides, Rosenberg and co-workers (76) had recourse to the reaction between tetravinyltin and tin(IV) chloride. In this way better yields of pure products were obtained. Alkylvinyltin compounds have been shown (76a) to react with α-halogenated acids (and related strong acids) with loss of ethene and the formation of esters.

$$R_nSn(CH{=}CH_2)_{4-n} + R'COOH \longrightarrow R_nSn(O_2CR')_{4-n} + C_2H_4$$

(R = CH_3, C_3H_7; R′ = CF_3, CCl_3, $CHCl_2$, CH_2Cl, CH_2Br, CH_2CN)

Like Seyferth, Rosenberg reports cleavage of the tin–carbon bond by the action of bromine and showed further that the ease of displacement is phenyl > vinyl > methyl > *n*-butyl. In this way he was able to prepare compounds of the types $C_6H_5(CH_2{=}CH)_2SnBr$ and $R_2(CH_2{=}CH)SnBr$.

Seyferth (80), taking advantage of the lability of the tin–vinyl bond, prepared the vinylmercury halides, $CH_2{=}CHHgX$ (X = Cl, Br, I), by the action of mercuric halides on vinyltin compounds. Like the vinylsilanes, monovinyltins react with polyhalogenomethanes and $SiHCl_3$ in the presence of benzoyl peroxide (81) to give the addition compounds $R_3SnCHXCH_2CCl_3$ (X = H, Cl, Br) and $R_3Sn(CH_2)_2SiCl_3$. However, they do not react with $SiHCl_3$ in the presence of platinized charcoal, nor do they add hydrogen in the presence of platinum.

Using vinylmagnesium bromide, Seyferth (83) was successful in preparing neopentylvinyltin compounds of the type bis(trimethylsilylmethyl)divinyltin, $[(CH_3)_3SiCH_2]_2Sn(CH{=}CH_2)_2$.

3. Vinylgermanes. Seyferth (82), once again utilizing vinylmagnesium bromide, has prepared several alkylvinylgermanium compounds such as diethyldivinylgermane and ethyltrivinylgermane. Whereas tin tetrachloride and tetrachlorosilane react with vinylmagnesium bromide to give only tetravinyltin and tetravinylsilane, respectively, germanium tetrachloride reacts with vinylmagnesium bromide to give a mixture of the expected tetravinylgermane and hexavinyldigermane (XIV). The latter reacts with the halogens to give the trivinylgermanium halide (XV).

$$\underset{\text{(XIV)}}{(CH_2{=}CH)_3GeGe(CH{=}CH_2)_3} \xrightarrow{X_2} \underset{\text{(XV; X = Br, I)}}{(CH_2{=}CH)_3GeX}$$

The vinylgermanes are much more stable to cleavage reactions than are the corresponding vinyltin compounds; thus, the vinyl group is not displaced by reaction with either germanium tetrachloride or mercuric chloride.

B. VINYL DERIVATIVES OF GROUP V ELEMENTS

Maier and co-workers (41) have prepared the trivinyl derivatives (XVI) of the group V elements by the action of vinylmagnesium bromide on the appropriate halide in tetrahydrofuran solution:

$$3CH_2{=}CHMgBr \xrightarrow{M^VX_3} \underset{\substack{\text{(XVI; M =}\\ \text{P, As, Sb, Bi)}}}{(CH_2{=}CH)_3M^V} + 3MgBrX$$

Vinylhaloarsines and vinylhalostibines of the type XVII (M = As and Sb, respectively) may be obtained by the action of the appropriate trihalide, M^VX_3, on trivinylarsine and trivinylstibine; vinylhaloarsines may also be obtained by the action of arsenic tribromide and trichloride on dialkyldivinyltin.

$$(CH_2{=}CH)_3M^V \xrightarrow{M^VX_3} \underset{\text{(XVII; X = Cl, Br)}}{(CH_2{=}CH)_nM^VX_{3-n}}$$

Trivinylarsine and trivinylstibine (XVI; M = As and Sb, respectively) react with iodine to give trivinylarsine and trivinylstibine diiodides, $(CH_2{=}CH)_3MI_2$, and these in turn undergo thermal decomposition to vinyl iodide and the corresponding divinyliodo derivatives, $(CH_2{=}CH)_2MI$.

C. VINYL DERIVATIVES OF MERCURY AND BORON

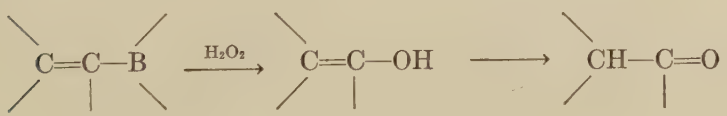
1. Vinylmercury Derivatives. By the action of vinylmagnesium bromide on HgX_2 (X = Cl, Br, I) in a 1:1 ratio, $CH_2{=}CHHgX$ can be prepared in high yield (1a; also described above, see ref. 80). These organomagnesium compounds can also be transformed into $CH_2{=}CHHgR$ (R = alkyl or aryl) by treatment with Grignard reagents. When the vinyl magnesium compound is used in excess over $HgCl_2$, divinylmercury is obtained in yields often exceeding 80% (1a,71a). This reagent is an interesting vinylation agent; it reacts with PCl_3 and BF_3 to furnish $CH_2{=}CHPCl_2$ and $CH_2{=}CHBF_2$, respectively.

2. Vinylboron Derivatives. Alkenylmagnesium halides react with alkyl borates or boron halides to give, depending upon the proportion of the reagents, mono- or dialkenylboric acids or boranes (66b). Several crystalline monoalkenylboric acids have been thus prepared.

Monoalkenylboric acid	Melting point, °C.
$CH_2{=}CHB(OH_2)$	74
$CH_3CH{=}CHB(OH)_2$	86–87
$CH_2{=}C(CH_3)B(OH)_2$	104
$(CH_3)_2C{=}CHB(OH)_2$	87

The monoalkenylboric acids combine with alcohols and glycols to furnish alkenyl borates, $\rangle C{=}CB(OR)_2$. The compounds with the groupings $CH_2{=}C(CH_3)-$ and $CH_2{=}CH-$ polymerize rapidly in the presence of air or oxygen. The alkenyl borates resemble the aryl borates in chemical behavior in that they are hydrolyzed to acids by warming with 5% sulfuric acid and to sodium alkenyl borates by warming with 5% sodium hydroxide.

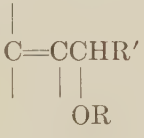
Ammoniacal silver nitrate causes decomposition, slowly in the cold and rapidly upon warming, to form the corresponding olefin with the precipitation of metallic silver. Hydrogen peroxide causes rupture of the boron–carbon link with the formation of the aldehyde or ketone.



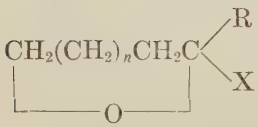
When this reaction is carried out in the presence of an alcoholic solution of 2,4-dinitrophenylhydrazine, the corresponding 2,4-dinitrophenylhydrazones are formed; this provides a useful procedure for the identification of the alkenyl groups attached to boron.

D. REACTIONS INVOLVING RUPTURE OF THE CARBON–HALOGEN BOND

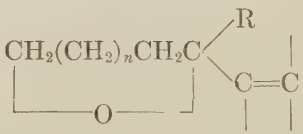
1. α-Halogeno Ethers (Table X-A). Alkenylmagnesium halides react readily with α-halogeno ethers, ROCHXR′, or with chloromethyl ethers, $ROCH_2Cl$, to give the corresponding α-ethylenic ethers (XVIII) (51). When this reaction is applied to α-halogenotetrahydrofurans or -pyrans (XIX; $n = 1$ and 2, respectively), the halogen atom is smoothly replaced by the alkenyl group to give XX ($n = 1$ and 2, respectively) (18).



(XVIII)



(XIX)

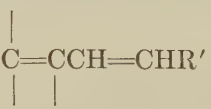


(XX)

2. α,β-Dihalogeno Ethers. α,β-Dihalogeno ethers of the type $ROCHXCH_2X$ are readily accessible from vinyl ethers, and the homologs of the type ROCHXCHXR′ may be prepared from the corresponding aldehydes, $R'CH_2CHO$. It is known that in this type of compound it is the α-halogen which enters into reaction with Grignard reagents, sometimes with concomitant loss of HX.

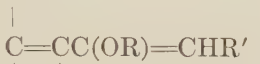
With alkenylmagnesium halides, the reaction products (50,63) are the corresponding α-alkoxy-β-halogenoalkenes (XXI) in yields ranging from 65 to 70% (Table X-B). These in turn may be converted to

(XXI)



(XXII)

conjugated dienes (XXII) by the action of powdered sodium in THF (50), a reagent superior to zinc in butanol. Elimination of HX from XXI to give the alkoxydienes (XXIII) can be effected (in 55–75% yield) by the action of KOH in diethylene glycol or, better (in 65–80% yield), by the action of KOH in *tert*-butanol.



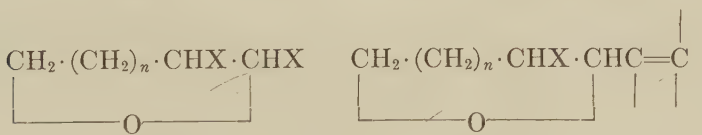
(XXIII)

The alkoxydienes (XXIII) are of considerable interest, for, on the one hand, they may be regarded as dienes, and on the other as dienophiles. Thus, on treatment with dilute mineral acid at −5° in an inert atmosphere, they undergo smooth hydrolysis to the *α,β-unsaturated ketones* (XXIV). This constitutes a new synthetic route to

(XXIV)

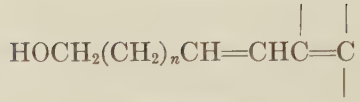
α,β-unsaturated ketones. It is not necessary to isolate the intermediate alkoxydiene; hydrolysis of the crude dehydrohalogenation product gives the α,β-unsaturated ketone in yields of the order of 50% (63) (Table X-C).

With cyclic α,β-dihalogeno ethers, such as 2,3-dihalogenotetrahydrofurans and -pyrans (XXV; n = 1 and 2, respectively), it is again the halogen atom in the α-position which reacts with Grignard reagents. Thus, with alkenylmagnesium halides, the products are the corresponding 2-alkenyl-3-halogenotetrahydrofurans and -pyrans (XXVI; n = 1 and 2, respectively). The latter are valuable synthetic



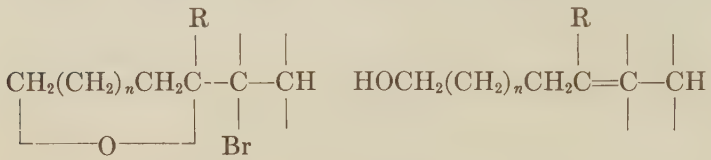
(XXV) (XXVI)

intermediates, for by the action of powdered sodium (54) (a now classical reaction (68)) they are converted to the *dienols* (XXVII).



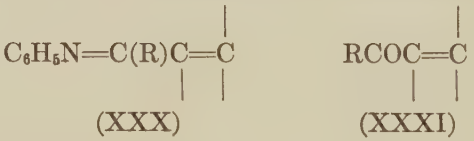
(XXVII)

Similarly, the β-bromo ethers (XXVIII; n = 1 and 2), which can be obtained by the action of HBr on 2-alkenyltetrahydrofurans or -pyrans (XX; n = 1 and 2, respectively), can be converted to the γ- or δ-ethylenic alcohols (XXIX; n = 1 and 2, respectively) (18). The over-all yields in this series of reactions are excellent, and it is not necessary to isolate the intermediate β-bromo ethers; a survey of the alcohols prepared in this way is given in Table X-D.



(XXVIII) (XXIX)

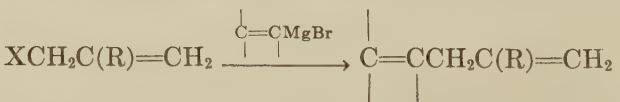
3. Imino Chlorides. Busch (10) was the first to show that organomagnesium halides will react with imino chlorides of the type $C_6H_5N{=}C(Cl)R$; furthermore, the reactivity of the halogen atom is such that it can be replaced by —OH. The action of alkenylmagnesium halides on imino chlorides leads to the formation (in 50% yield) of ketenimines (XXX); these, in turn, can be hydrolyzed to the α,β-unsaturated ketones (XXXI) (62). For a survey of the compounds prepared



(XXX) (XXXI)

in this way see Table X-C.

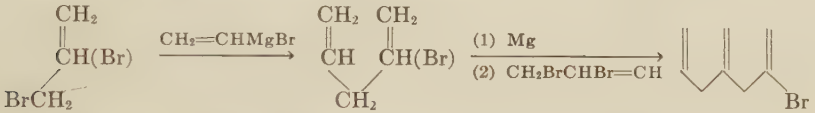
4. Allylic Halides. The careful addition of an alkenylmagnesium halide to a hot solution of an allyl halide, $XCH_2C(R){=}CH_2$, leads to the formation in good yield of *1,4-dienes* (XXXII) (Table X-E).



(XXXII)

Normal addition leads to isomerized products and products formed from secondary reactions involving the central methylene group (50). With homologous allyl bromides, the course of the reaction is no longer unambiguous, and the product consists of mixtures of dienes containing a preponderance of the branched chain isomers.

2-Bromoallyl bromide reacts with vinylmagnesium bromide to give 2-bromopenta-1,4-diene, and this in turn, being an alkenyl bromide, should be capable of reacting with magnesium to give the organomagnesium halide. The latter has not been prepared nor have its reactions been investigated. However, it should react with 2-bromoallyl bromide according to the scheme



We have here a possible new synthetic route to polyenes which merits further investigation.

4-Chlorobut-2-en-1-ol with excess propenylmagnesium halide gives *hepta-2,5-diene-1-ol*, $CH_3CH{=}CHCH_2CH{=}CHCH_2OH$, in 71% yield, (54).

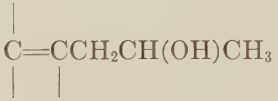
In contrast to the allyl halides, it would seem that benzyl halides react with difficulty; thus, the action of vinylmagnesium bromide on benzyl chloride gives substantial quantities of 1,2-diphenylethane and little allylbenzene. Vinylmagnesium bromide reacts with propargyl bromide to give a mixture of the enyne $CH_2{=}CHCH_2C{\equiv}CH$ (40% yield) and the triene $CH_2{=}CHCH{=}C{=}CH_2$ (60%), which can be separated by chemical methods (44a).

E. REACTIONS INVOLVING RUPTURE OF THE CARBON–OXYGEN BOND

1. Ethyl Orthoformate (Table XI-A). The reaction of Bodroux-Tchitchibabin has not been extensively studied with alkenylmagnesium halides. With the magnesium derivatives of primary alkenyl bromides, RCH=CH Br, the yields are poor; in the case of secondary alkenyl bromides, $RCBr{=}CH_2$, the yields are in the order of 50% (55). The products in the latter instance are *acetals of α-substituted acroleins*, $CH_2{=}C(R)CH(OC_2H_5)_2$, which, when treated with 2,4-dinitrophenylhydrazine in acid solution, are smoothly converted to the corresponding 2,4-dinitrophenylhydrazones.

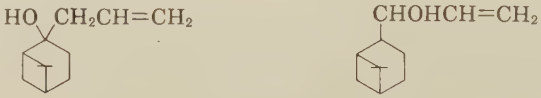
2. 1,2-Epoxides (Table XI-B). To date the action of alkenylmagnesium halides on 1,2-epoxides, a reaction which should lead to β-ethylenic alcohols, has not been studied systematically. However, it has been shown that certain of these Grignard reagents react with ethylene oxide to give the *primary alcohols* (XXXIII) and with propylene oxide to give the *secondary alcohols* (XXXIV) (52). Primary β-ethylenic alcohols with substituents in the γ-position, $RCH{=}CH{-}CH_2CH_2OH$, may also be prepared in excellent yield by the reaction of 2-alkyl-3-chlorotetrahydrofurans with powdered sodium (47). These two methods together render accessible a large variety of substituted β-ethylenic alcohols.

(XXXIII)

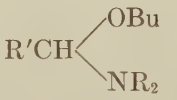


(XXXIV)

In an effort to prevent isomerizations, which are known to be occasioned by the presence of magnesium halides, pure divinylmagnesium (prepared by precipitation of $MgBr_2$ with dioxane from a THF solution of vinylmagnesium bromide) was allowed to react with the epoxide of β-pinene. However, instead of the expected tertiary alcohol, an isomeric secondary alcohol was obtained which was assigned the structure shown below (84a).



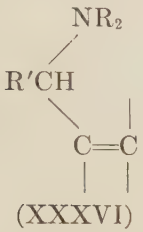
3. Dialkylamino Ethers (Tables XI-C and XI-D). Dialkylamino ethers of the type XXXV are readily prepared by the base-catalyzed condensation of the secondary amine, R_2NH, formaldehyde (or aromatic aldehyde), and butanol in butanol solution. Such ethers react



(XXXV; R′ = H or aryl)

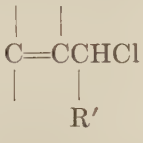
with Grignard reagents to give the tertiary amines (72), and with alkenylmagnesium halides they undergo a similar reaction to give the corresponding unsaturated *tertiary amine* (XXXVI) (19) (Table XI-C).

164181-57

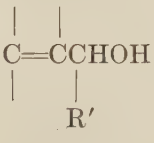


(XXXVI)

This simple and direct synthesis is superior to the alternative one involving the action of a secondary amine, R_2NH, on an allyl halide (XXXVII), since it avoids the possible rearrangements which at times accompany the latter. Furthermore, the preparation of the allyl halide (XXXVII) from the corresponding alcohol (XXXVIII) is in itself a delicate reaction. The reaction, when applied to 2-dialkyl-

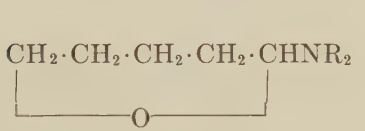


(XXXVII)

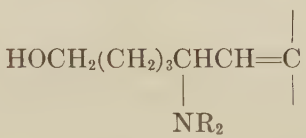


(XXXVIII)

aminotetrahydropyrans (XXXIX) gives amino alcohols of the type XL. Other cyclic ethers containing an α-alkylamino group such as

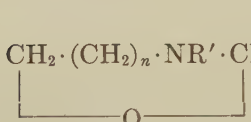


(XXXIX)

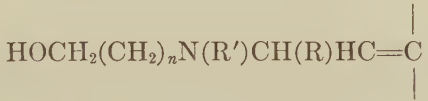


(XL)

oxazolidines and tetrahydrometoxazines (XLI; $n = 1$ and 2, respectively) react with alkenylmagnesium halides to give amino alcohols of the type XLII (Table XI-D). This is in keeping with Senkus' earlier observations (77) on their reaction with alkylmagnesium halides.



(XLI)

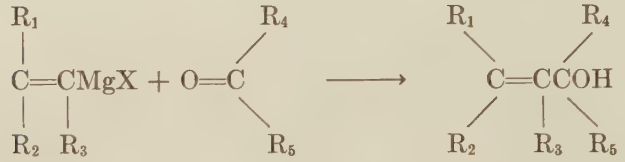


(XLII)

A/547

F. REACTIONS WITH ALDEHYDES AND KETONES

1. Nonethylenic Aldehydes and Ketones. The action of alkenylmagnesium halides on carbonyl compounds constitutes the most convenient and general synthetic route to *α-ethylenic alcohols* (XLIII) (51).



(XLIII)

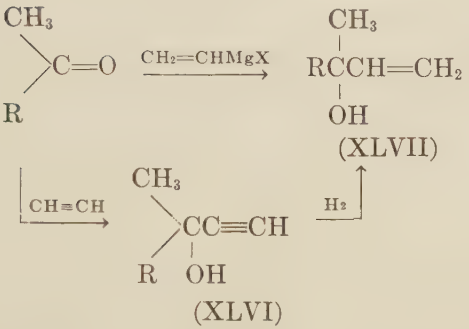
The yields are excellent (see Tables XII-A and XII-B), provided an excess (10–20%) of organomagnesium halide is used and the reaction is carried out slowly at low temperatures (0 to −10°). These precautions are necessary in order to obviate the usual side reactions, namely, self-condensation of the carbonyl component and oxidation-reduction reactions due to the presence of magnesium alkoxides. The present method is superior to the older classical synthesis from α,β-unsaturated aldehydes and ketones since it avoids the abnormal reactions associated with the latter (1,4-addition of the Grignard reagent, etc.). Furthermore the α,β-unsaturated aldehydes and ketones are themselves not readily accessible compounds.

The scope of the synthetic method is exemplified by the following:

1. The preparation of the difficultly accessible alkyl alcohols (XLIV) which in turn are smoothly isomerized to the ketones (XLV) by heating with Raney nickel.

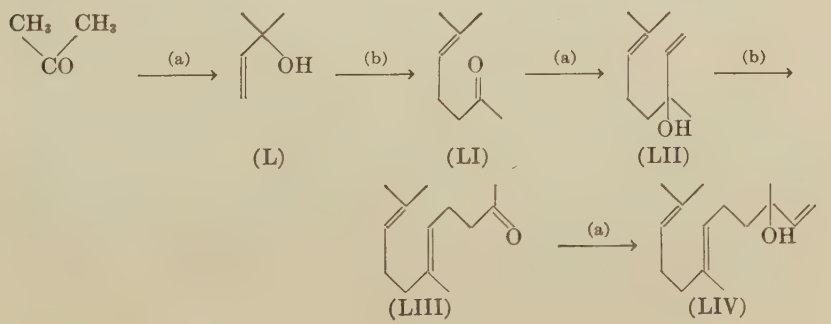
$$CH_2{=}C(R')MgX \xrightarrow{RCHO} \underset{(XLIV)}{RCH(OH)C(R'){=}CH_2} \longrightarrow \underset{(XLV)}{RCOCH(R')CH_3}$$

2. The one-step preparation of the tertiary alcohols (XLVII). The present method eliminates the partial reduction involved in the alternative synthesis via the acetylenic carbinol (XLVI).



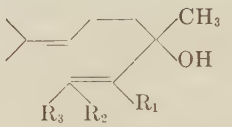
3. The preparation of the homologous unsaturated tertiary alcohols (XLVIII and XLIX). It will be noticed that whereas alcohols of the type XLVIII may be prepared by an alternative synthesis (condensation of the carbonyl compound with the appropriate acetylene and partial reduction of the product), such is not the case for alcohols of the type XLIX. The present method thus constitutes the only convenient synthetic route to such compounds.

Carroll (11) has shown that it is possible to convert the allylic alcohol (L) to the γ-ethylenic ketone (LI). By a combination of the Normant reaction (a) and the Carroll reaction (b) the total synthesis of the isoprenoid alcohols linaloöl (LII) and nerolidol (LIV) has been effected.



The intermediate ketones are methylheptenone (LI) and geranylacetone (LIII) and the yields obtained in the Normant reaction are all in the neighborhood of 80%.

The homologs (LV) of linaloöl which have been synthesized in this way (53), together with the organomagnesium compounds used, are shown in Table III.



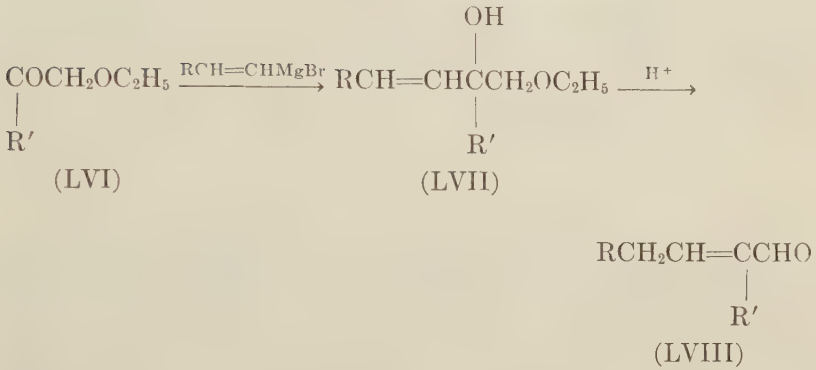
(LV)

TABLE III

Organomagnesium compound	Product (LV)			Yield, %
	R_1	R_2	R_3	
CH_2=CHMgBr	H	H	H	83
CH_3CH=CHMgBr	H	H	Me	60
CH_2=C(CH_3)MgBr	CH_3	H	H	68
$(CH_3)_2C$=CHMgBr	H	CH_3	CH_3	61
n-$C_5H_{11}CH$=CHMgBr	H	H	n-C_5H_{11}	65

2. α-Alkoxy Ketones. Behal and Sommelet (1) record the fact that the monoethers of primary-tertiary glycols may be converted by the action of formic acid to the aldehyde.

$$RCH_2C(OH)CH_2OR \longrightarrow RCH_2CH(R)CHO$$
$$\quad\quad\quad



This represents a convenient synthetic route to *α,β-unsaturated aldehydes* and the yields in the last step range from 75 to 80%.

A survey of the monoethers of primary-tertiary glycols prepared in this way, together with the reagents used, is given in Table IV.

TABLE IV

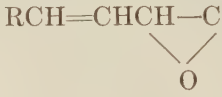
R in RMgX	R′ in LVI	Product (LVII)	Yield, %
CH_2=CH—	*n*-C_7H_{15}	CH_2=CHC(C_7H_{15})(OH)$CH_2OC_2H_5$	61
CH_3CH=CH—	CH_3	CH_3CH=CHC(CH_3)(OH)$CH_2OC_2H_5$	43
CH_3CH=CH—	*n*-C_4H_9	CH_3CH=CHC(C_4H_9)(OH)$CH_2OC_2H_5$	50
CH_3CH=CH—	*n*-C_7H_{15}	CH_3CH=CHC(C_7H_{15})(OH)$CH_2OC_2H_5$	85

3. α-Halogeno Aldehydes, α-Halogeno Ketones, and Chloral. A detailed study of the action of alkenyl halides on α-halogeno aldehydes and ketones has not been made to date. However, it has been shown (55) that propenylmagnesium bromide reacts with monochloracetone to give a 40% yield of the chlorohydrin:

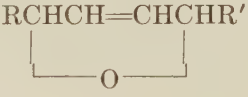
$$CH_3COCH_2Cl \xrightarrow{CH_3CH=CHMgBr} CH_3CH=CHC(Me)(OH)CH_2Cl$$

The reaction with α-chloro aldehydes proceeds normally to give the *ethylenic chlorohydrins*, RCH=CHCH(OH)CH(Cl)R′ (LXIV), free from the isomers, RCH(OH)CH=CHCH(Cl)R′, since, on treatment with solid KOH or $NaNH_2$ in ether, they give the *ethylenic oxide* (LIX) free from any trace of the dihydrofurans (LX). These ethylenic ep-

oxides are capable of many synthetic applications; their hydration to glycols, RCH=CHCH(OH)CH(OH)R′, and their reaction with secondary amines have been investigated (61).



(LIX)



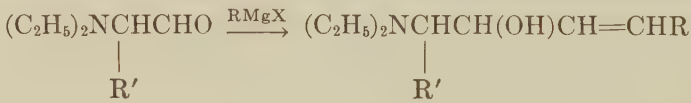
(LX)

Whereas arylmagnesium halides react normally with chloral, alkylmagnesium halides may at times react as reducing agents, yielding up to 50% of trichloroethanol (26). Alkenylmagnesium halides, which can be considered as having a structural resemblance to the arylmagnesium halides, react with chloral to give the *trichloromethylvinyl carbinols* (LXI) (58) (Table XII-C). Alcohols of this type may

(LXI)

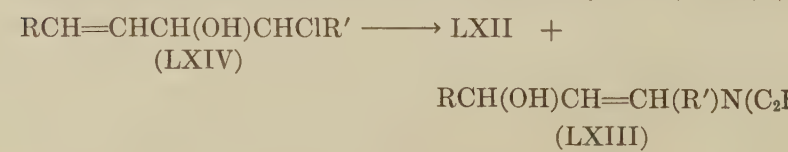
also be prepared by the straightforward condensation of chloral and an olefin in the presence of a Lewis acid. However, the presence of the Lewis acid can occasion subsequent isomerization of the double bond (13), and in such cases the former, less direct method is preferable.

4. Amino Aldehydes and Amino Ketones (Table XII-D). α-Dialkylamino aldehydes, which are readily obtainable by the method of Kirrmann (36), react normally with alkenylmagnesium halides to give the corresponding secondary amino alcohols (LXII). These



(LXII)

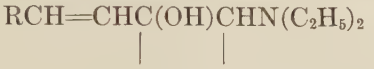
compounds, together with the isomers (LXIII), may also be obtained by the action of secondary amines on the chlorhydrins (LXIV) (56).



(LXIV)

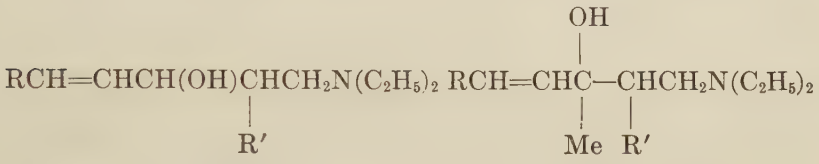
(LXIII)

The tertiary amino alcohols (LXV) have been prepared in an analogous manner from α-dialkylamino ketones. The action of alkenyl-



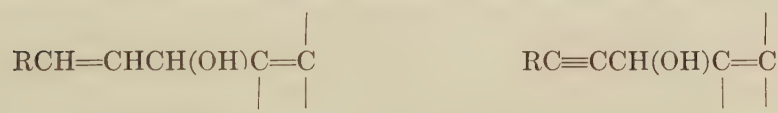
(LXV)

magnesium halides on Mannich bases results in the formation of secondary or tertiary dialkylamino alcohols (LXVI or LXVII).



(LXVI) (LXVII)

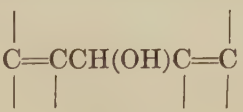
5. α-Ethylenic Aldehydes and Ketones (Table XII-E). Previously the only method available for the preparation of α,α′-diethylenic alcohols of the general structure LXVIII involved the partial hydrogenation of the carbinols (LXIX). The latter were in turn obtained by the condensation of an acetylenic Grignard with the appropriate aldehyde or ketone. More recently Jones and associates (29) de-



(LXVIII) (LXIX)

scribed the preparation of acetylenemagnesium bromide in THF, and it was thus possible to prepare the lower homologs of this series of acetylenic alcohols (LXIX; R = H).

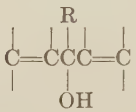
Once again the use of alkenylmagnesium halides in this field has not only greatly simplified the preparation of these compounds but also made available more highly substituted alcohols. Thus, reaction with α,β-unsaturated aldehydes gives directly the α,α′-diethylenic carbinols



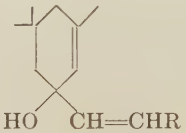
(LXX)

(LXX) (2,54). The symmetrically substituted alcohols can also be obtained by the interaction of an alkenylmagnesium halide and ethyl formate (54). In the cases studied (54,59) the addition of the Grignard reagent would appear to occur on the carbonyl function to the exclusion of 1,4-addition, though a thorough investigation of the reaction is called for. The anionotropic rearrangement of the α,α'-diethylenic alcohols has been extensively studied by Raphael (71).

Tertiary alcohols of the type LXXI and in particular those derived from isophorone, e.g., LXXII (R = H and CH_3), are readily dehydrated to trienes (59).

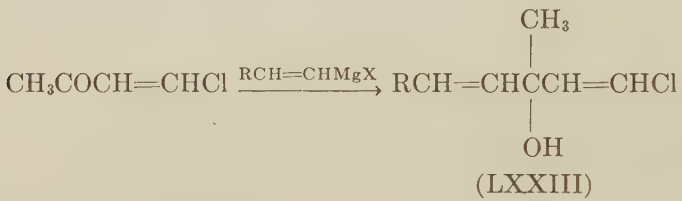


(LXXI)



(LXXII)

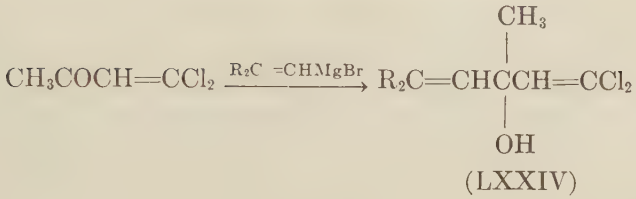
6. Reaction with Halogenoethylenic Ketones. Alkenylmagnesium halides react with methyl chlorovinyl ketone to give the chlorodiethylenic alcohols (LXXIII) (65):



(LXXIII)

An alcohol of this type (R = H) had previously been prepared by M. Julia (30) by the partial hydrogenation of the corresponding acetylenic alcohol with a view to generalizing the reaction of Jones and Weedon (28). Anionotropic rearrangement of this carbinol does not give the diethylenic aldehyde, $CH_2{=}CHC(CH_3){=}CHCHO$, but the alcohol, $CH_2OHCH{=}C(CH_3)CH{=}CHCl$. A detailed study of other examples of this rearrangement has yet to be made.

Julia and Surzur (31), by the action of alkenylmagnesium halides on methyl dichlorovinyl ketone, obtained the alcohols (LXXIV; R = H, CH_3) which they were able to convert to the unsaturated acids (LXXV; R = H, CH_3).



(LXXIV)

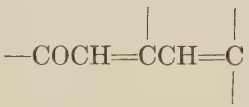
$$R_2C{=}CHC(CH_3){=}CHCOOH$$

(LXXV)

The alcohol $CH_2{=}CHCHOHCH{=}CCl_2$ has been prepared in approximately 70% yield from $CH_2{=}CHMgBr$ and $CCl_2{=}CHCHO$ by Julia and Bullot (31a).

7. 1,3-Diketones. 1,3-Diketones in which one of the carbonyl groups is protected ($-$[CO]—) react smoothly with alkenylmagnesium halides. When the addition complex (LXXVI) is treated with mineral acid, the carbonyl function is liberated from the protective group, and the molecule undergoes dehydration to give the *dienone* (LXXVII) (14).

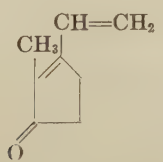
(LXXVI)



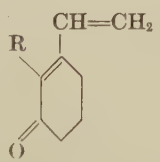
(LXXVII)

This excellent synthetic method has been used to prepare the dienones listed in Table XII-F.

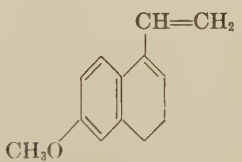
The application of this synthesis to cyclic β-diketones offers a new route to compounds of value in the synthesis of steroids which avoids the partial hydrogenation associated with the use of acetylenic compounds (17). Some of the compounds prepared in this way are LXXVIII–LXXX.



(LXXVIII (14))



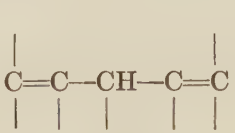
(LXXIX (14,46,67))



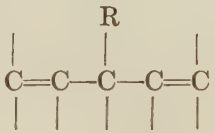
(LXXX (46))

G. REACTIONS WITH ACID DERIVATIVES AND CARBON DIOXIDE

1. Saturated and Unsaturated Esters. As has already been mentioned, the action of alkenylmagnesium halides with the esters of formic acid results in the formation of the symmetrical *α,α′-diethylenic secondary alcohols* (LXXXI). With other saturated aliphatic esters the product is the *α,α′-diethylenic tertiary alcohol* (LXXXII) (54) (Table XIII-A).

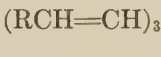


(LXXXI)

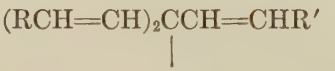


(LXXXII)

Normant and Maitte (59) have prepared several previously unknown *α,α′,α″*-triethylenic alcohols; the fully symmetrical ones (LXXXIII) were prepared from ethyl carbonate and the others (LXXXIV) from the corresponding *α,β*-unsaturated esters. The yields obtained were in general good, the exception being the reactions involving vinylmagnesium bromide (LXXXIV; R = H) (Table XIII-B).

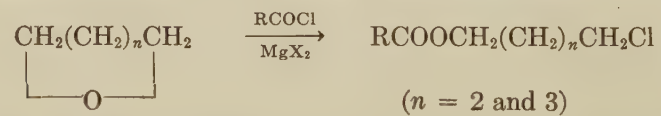


(LXXXIII)



(LXXXIV)

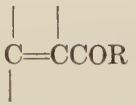
2. Acid Chlorides. The fact that the alkenylmagnesium halides have to be prepared in THF, its homologs, or tetrahydropyran is in itself a complication in their reactions with acid chlorides. The latter, in the presence of magnesium halides, bring about opening of the cyclic ether ring even at 0° (60) to give the *ω*-chloro esters.



(*n* = 2 and 3)

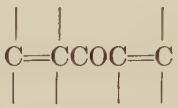
Since the organomagnesium halides are strongly solvated, the replacement of the solvent by another higher boiling and less basic

one (e.g., anisole or phenetole) does not result in any significant improvements. However, by operating at $-40°$ and by adding the organomagnesium compound slowly to the acid chloride, it is possible to obtain the *α,β-unsaturated ketones* (LXXXV) in yields of around 40% (43).



(LXXXV)

3. Acid Anhydrides. The complications which are inherent in the use of acid chlorides are not encountered in the case of acid anhydrides since the latter have little or no effect on cyclic ethers. Thus, the addition of an alkenylmagnesium halide to an excess of an acid anhydride at $-60°$ results in the formation of an α,β-unsaturated ketone in yields ranging from 60 to 80% (43) (Table XIII-C). G. Martin prepared the *α,α′-diethylenic ketones* of the type LXXXVI from the unsaturated acid anhydride. Depending on the precise reagents used,



(LXXXVI)

the diolefinic ketone can be symmetrical or otherwise. He further showed that the use of sodium or lithium in the place of magnesium gives the *α-acetylenic ketone* irrespective of the solvent used (ether or tetrahydrofuran).

4. N,N-*Disubstituted Amides:* (*a*) *Formamides.* It is known from the work of Bouveault that the action of organomagnesium compounds on formamides can produce either an aldehyde or a tertiary amine when the reaction is carried out by heating in the presence of excess magnesium. The formation of secondary alcohols is rarely observed and is always slow. Contrary to the behavior of alkyl formates, this is due to the stability of the addition complex, which decomposes in the cold to an aldehyde by treatment with water and to an amine by warming with excess Grignard reagent.

$$RMgX + (R',R'')NCHO \longrightarrow$$

$$(R',R'')NCH(OMgX)R \xrightarrow{H_2O} RCHO + (R',R'')NH$$

$$\Big\downarrow RMgX$$

$$(R',R'')NCHR_2 + MgX_2 + MgO$$

The more basic alkenyllithium compounds furnish little aldehyde but form condensation products instead (9).

By contrast, vinylmagnesium compounds have been shown to behave normally (19a). The slow addition of one mole of the magnesium compound to a cold solution of one mole of the formamide in THF furnishes an α,β-unsaturated aldehyde.

$$\diagdown C{=}C(MgX) + HCON(R,R') \longrightarrow \diagdown C{=}CCHO + HN(R,R')$$

Some results are shown in Table V.

When the formamide is added to an excess of the magnesium compound without cooling, an amine (i.e., $(CH_3CH{=}CH)_2CHN(CH_3)_2$ from experiment 3 in Table V) is formed.

Vinylogous formamides, $HCOCH{=}CHN(R,R')$, behave similarly. By the addition of the magnesium compound in the cold, an aldehyde is obtained (31b).

$$C_6H_5MgBr + HCOCH{=}CHN(CH_3, C_6H_5) \longrightarrow$$

$$C_6H_5CH{=}CHCHO \qquad (35\%)$$

The following reaction generally fails to give $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes in satisfactory yield.

$$\diagdown C{=}C(MgBr) + HCOCH{=}CHN(R,R') \longrightarrow$$

$$\diagdown C{=}CCH{=}CHCHO$$

TABLE V

Experiment	R in RMgX (A)	HCONR′R″ (B) R′	HCONR′R″ (B) R″	Ratio A/B	Condens. temp., °C.	Product	Yield, %
1	CH_2=C(CH_3)	CH_3	CH_3	1	−60	CH_2=C(CH_3)CHO	[a]
2	CH_3CH=CH	CH_3	CH_3	1	−60	CH_3CH=CHCHO	23[b]
3	CH_3CH=CH	CH_3	CH_3	2	+20	Amine	38
4	$(CH_3)_2$C=CH	CH_3	CH_3	1	−60	$(CH_3)_2$C=CHCHO	23
5	$(CH_3)_2$C=CH	C_2H_5	C_6H_5	1	−60	$(CH_3)_2$C=CHCHO	40
6	$(CH_3)_2$C=CH	C_2H_5	C_6H_5	1	−15	$(CH_3)_2$C=CHCHO	40
7	$(CH_3)_2$C=CH	C_6H_5	C_6H_5	1	−60	$(CH_3)_2$C=CHCHO	44
8	$(CH_3)_2$C=CH	C_2H_5	C_6H_5	2	−60	$(CH_3)_2$C=CHCHO	56
9	$C_6H_{13}CH$=CH	C_2H_5	C_6H_5	1	−15	$C_6H_{13}CH$=CHCHO	62
10	$C_6H_5C(CH_3)$=CH	C_2H_5	C_6H_5	1	−15	$C_6H_5C(CH_3)$=CHCHO	60

[a] The aldehyde which was dissolved in the solvent was shown to be present by the formation of its 2,4-DNPH (m.p. 238°).
[b] Yield of isolated aldehyde, characterized by the formation of its 2,4-DNPH (m.p. 197°) from material dissolved in the filtrate.

TABLE VI

Organomagnesium halide	Amide	Ketone	Yield, %
$CH_3CH{=}CHMgBr$	$CH_3CON(C_2H_5)_2$	$CH_3CH{=}CHCOCH_3$	0
$CH_3CH{=}CHMgBr$	$C_3H_7CON(C_2H_5)_2$	$CH_3CH{=}CHCOC_3H_7$	20
$CH_3CH{=}CHMgBr$	$C_3H_7CON(C_2H_5)(C_6H_5)$	$CH_3CH{=}CHCOC_3H_7$	42
$CH_3CH{=}CHMgBr$	$C_3H_7CON(C_6H_5)_2$	$CH_3CH{=}CHCOC_3H_7$	26
$CH_3CH{=}CHMgBr$	$(CH_3)_3CCON(C_2H_5)(C_6H_5)$	$CH_3CH{=}CHCOC(CH_3)_3$	26
$CH_3CH{=}CHMgBr$	$C_6H_{13}CON(C_2H_5)(C_6H_5)$	$CH_3CH{=}CHCOC_6H_{13}$	32
$CH_3CH{=}CHMgBr$	$C_6H_5CON(C_2H_5)(C_6H_5)$	$CH_3CH{=}CHCOC_6H_5$	43
$CH_3CH{=}CHMgBr$	$C_6H_5CH_2CON(C_2H_5)(C_6H_5)$	$CH_3CH{=}CHCOCH_2C_6H_5$	24
$(CH_3)_2C{=}C(CH_3)MgBr$	$C_3H_7CON(C_2H_5)(C_6H_5)$	$(CH_3)_2C{=}C(CH_3)COC_3H_7$	28

However, by warming with an excess of the vinylmagnesium halide, an unsaturated amine is formed.

$$CH_3CH{=}CHMgBr + HCOCH{=}CHN(CH_3)_2 \longrightarrow$$

$$(CH_3CH{=}CH)_2CHCH{=}CHN(CH_3)_2$$

(*b*) *Other amides.* The reaction of vinylmagnesium bromides with *N*,*N*-disubstituted amides under various reaction conditions leads to α,β-unsaturated ketones although not in satisfactory yield (44) (see Table VI).

Benary (1c) has reported that Grignard reagents react with unsaturated amino ketones to form α,β-unsaturated ketones, probably by 1,4-addition. When THF is used as a solvent rather than ether, the yields are considerably improved. The reaction has been extended to vinylmagnesium compounds with excellent results and leads to $\alpha,\beta,\gamma,\delta$-unsaturated ketones (14a).

$$RCOCH{=}CHN\!\!\diagup\!\!\diagdown + R'MgX \longrightarrow RCOCH{=}CHR' \quad (5)$$

(R′ = alkyl or aryl)

A few examples of this reaction are given in Table VII.

TABLE VII

R in eq. 5	R′ in eq. 5	Ketone	Yield, %
CH_3	$CH_2{=}CH$	$CH_3COCH{=}CHCH{=}CH_2$	Polymerization
CH_3	$CH_3CH{=}CH$	$CH_3COCH{=}CHCH{=}CHCH_3$	82
C_3H_7	$CH_3CH{=}CH$	$C_3H_7COCH{=}CHCH{=}CHCH_3$	74
C_6H_5	$CH_3CH{=}CH$	$C_6H_5COCH{=}CHCH{=}CHCH_3$	68
CH_3	$CH_2{=}C(CH_3)$	$CH_3COCH{=}CHC(CH_3){=}CH_2$	72
CH_3	$(CH_3)_2C{=}CH$	$CH_3COCH{=}CHCH{=}C(CH_3)_2$	88

By use of acetylenic Grignards a continual repetition of the process is possible.

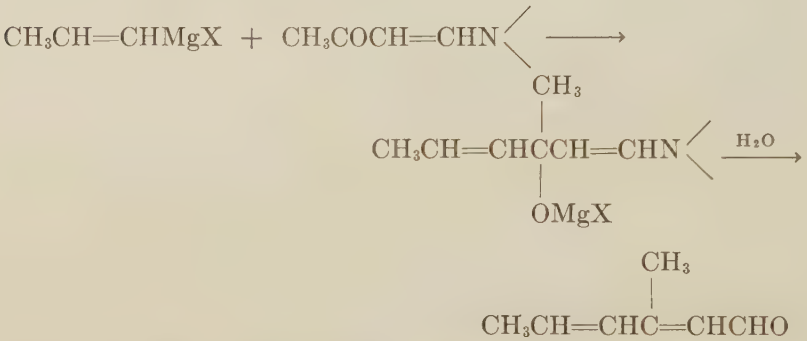
$$RCOCH{=}CHN\!\!\diagup\!\!\diagdown \xrightarrow{CH{\equiv}CMgX} RCOCH{=}CHC{\equiv}CH \xrightarrow{HN\!\diagup\!\diagdown}$$

$$RCOCH{=}CHCH{=}CHN\!\!\diagup\!\!\diagdown \xrightarrow{\text{repeat}} RCO(CH{=}CH)_nN\!\!\diagup\!\!\diagdown$$

Ketones can be prepared by treatment of these amines with vinylmagnesium halides

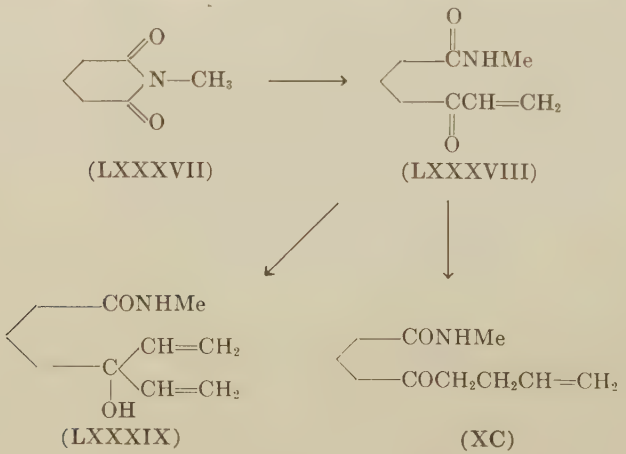
$$RCO(CH{=}CH)_nN\!\!<\!\!\!> + R'CH{=}CHMgX \longrightarrow RCO(CH{=}CH)_{n+1}R'$$

and in this way 2,4,6-undecatrien-8-one, $CH_3(CH{=}CH)_3COC_3H_7$, has been prepared. Normal addition to the carbonyl group would lead to an isomeric aldehyde, but the very slow rate of this reaction, coupled with the high yield of ketone obtained, has not permitted positive verification of this reaction course.



$$CH_3CH{=}CHMgX + CH_3COCH{=}CHN\!\!<\!\!\!> \longrightarrow CH_3CH{=}CHC(CH_3)(OMgX)CH{=}CHN\!\!<\!\!\!> \xrightarrow{H_2O} CH_3CH{=}CHC(CH_3){=}CHCHO$$

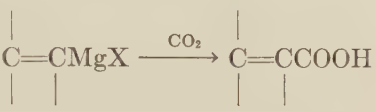
5. Miscellaneous Reactions. The action of vinylmagnesium bromide on *N*-methylglutarimide (LXXXVII) has recently been reported



(LXXXVII) → (LXXXVIII); (LXXXVIII) → (LXXXIX); (LXXXVIII) → (XC)

(12,12a). The products isolated are the methylamide of 5-hydroxy-5-ninylhept-6-enoic acid (LXXXIX) and the methylamide of 5-keto-von-8-enoic acid (XC) in the ratio of 1:2. The latter doubtless arises from 1,4-addition of vinylmagnesium bromide to the intermediate (LXXXVIII).

6. Carbon Dioxide and Phenyl Isocyanate. The carbonation of alkenylmagnesium halides by means of carbon dioxide suspended in ether forms an excellent method for the preparation of *α-ethylenic acids* (XCI) (60).



(XCI)

The high yields obtained in the preparation of tiglic and angelic acids (Table XIII-D) indicate that side reactions (i.e., formation of ketones and alcohols) are negligible.

It has been proved that both the formation of the alkenylmagnesium halide and its subsequent reactions proceed without any stereochemical change. Similar conclusions had already been reached by Braude and Timmons (3) and later by Dreiding and Pratt (16) for the lithium alkenyls (see also refs. 12b,46a).

7. Phenyl Isocyanate. Isocyanates rank equal to carbon dioxide as a means of identifying alkenyl halides. The action of phenyl isocyanate on the derived magnesium compounds takes place without any stereochemical change to give the corresponding crystalline *anilide* (XCII) (57).

(XCII)

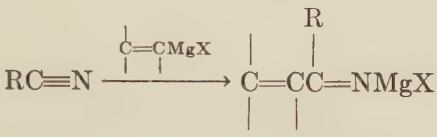
H. REACTIONS WITH SOME NITROGEN-CONTAINING COMPOUNDS

1. Nitriles. Aliphatic and aromatic nitriles react with alkenylmagnesium halides to give condensation products, the structures of which have still to be elucidated. They do not arise by self-condensa-

TABLE VIII

Organomagnesium halide	Schiff's base	Product	Yield, %
$CH_3CH{=}CHMgBr$	$C_6H_5CH{=}NC_6H_5$	$CH_3CH{=}CHCH(C_6H_5)NHC_6H_5$	64
$CH_3CH{=}CHMgBr$	$C_6H_5CH{=}N{-}n\text{-}C_4H_9$	$CH_3CH{=}CHCH(C_6H_5)NHC_4H_9$	75
$\begin{matrix}CH_3\\ \diagdown\\ C{=}CHMgBr\\ \diagup\\ CH_3\end{matrix}$	$C_6H_5CH{=}N{-}n\text{-}C_4H_9$	$(CH_3)_2C{=}CHCH(C_6H_5)NHC_4H_9$	50
$CH_3CH{=}C(CH_3)MgBr$	$C_6H_5CH{=}N{-}n\text{-}C_4H_9$	$CH_3CH{=}C(CH_3)CH(C_6H_5)NHC_4H_9$	43

tion of the nitrile, but result from reactions involving the unstable imine (XCIII).

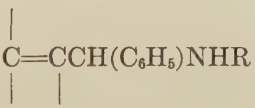


(XCIII)

From the reaction of propenylmagnesium bromide and benzonitrile it has been possible to isolate the imine $CH_3CH{=}CHC(C_6H_5){=}NH$ (m.p. 135), together with other nitrogen-containing materials (65). It would appear that this reaction will not constitute a very practicable synthesis of α,β-unsaturated ketones.

2. Schiff's Bases. In contrast to alkylmagnesium halides, alkenylmagnesium halides react normally with the —CH=N— system present in Schiff's bases. The reaction proceeds smoothly with benzalaniline, $C_6H_5CH{=}NC_6H_5$, but difficulties are encountered with compounds of the type $C_6H_5CH{=}NR$. It has been shown that this difference is not attributable to the organometallic compound used, but is due rather to the basicity of the solvent used (e.g., THF).

A variety of ethylenic secondary amines (XCV) have been prepared in this way (19). The various alkenylmagnesium halides and Schiff's bases used are tabulated in Table VIII.



(XCV)

III. Experimental

A. PREPARATION OF VINYLMAGNESIUM HALIDES (61)

1. General Method. The apparatus required is that used in the normal Grignard reaction; the usual precautions should be taken, though the use of dry nitrogen offers no special advantages.

Fine magnesium turnings (0.1 g.-atom) and tetrahydrofuran (25–30 ml.) are placed in the flask together with a trace of iodine (or mercuric chloride or a few drops of ethyl bromide or methyl iodide, etc.); the vinyl halide (0.5 ml.) is then added. The start of the exothermic

reaction is indicated by the disappearance of the iodine color and the appearance of a light brown color. If the reaction does not start immediately, the reagents should be gently warmed and no further halide added until it has.

Once the reaction has begun, the stirrer is started, and the vinyl halide (0.1 mole) in tetrahydrofuran (25–30 ml.) added at such a rate that the temperature of the reactants is maintained between 40 and 50°. When the addition is complete, the reaction mixture is heated at 70–80° for a further $^1/_2$–1 hr.; by the end of this time all the metal has dissolved leaving a clear pale brown solution. Stirring is continued and the reaction mixture allowed to cool; in this way a fine suspension of the vinylmagnesium halide will be obtained. If the stirring is not continued, the organometallic compound will set to a solid crystalline mass on cooling.

2. Particular Cases. For the preparation of vinylmagnesium bromide, the vinyl bromide is dissolved in an equal weight of THF.

For the preparation of vinylmagnesium chloride, a solution of vinyl chloride (1 mole) in THF (2 moles) should be used (see also 74).

In both cases it is preferable to replace the conventional reflux condenser by a dry ice condenser.

B. VINYL(TRI-*n*-BUTYL)TIN (78)

Vinyl bromide (61 g., 0.61 mole) was added to magnesium turnings (14.6 g., 0.61 g.-atom) in tetrahydrofuran (500 ml.), which had been distilled from lithium aluminum hydride to remove water and peroxides. A dry ice condenser was used and the addition of a few drops of methyl iodide sufficed to initiate the reaction. When the Grignard preparation was completed, the condenser was replaced with a water condenser and tri-*n*-butyltin chloride (107.5 g., 0.33 mole), dissolved in an equal volume of tetrahydrofuran, was added at such a rate that a gentle reflux was maintained. After the addition was complete, the reaction mixture was refluxed for a further 19 hr. It was subsequently cooled to room temperature and hydrolyzed by the addition of a saturated aqueous solution of ammonium chloride (100 ml.).

The orange organic layer was decanted and the residual salts washed with several portions of diethyl ether. The ether washings were combined with the organic layer and the mixture distilled at atmospheric pressure to remove solvents. The residue was fraction-

ally distilled under reduced pressure. In this manner, vinyl(tri-*n*-butyl)tin was obtained (84 g., 84.5% yield).

C. (±)-LINALOÖL (53)

2-Methylhept-2-en-6-one (101 g., 0.8 mole) in an equal volume of dry ether was added over a period of 1 hr. to a stirred suspension of vinylmagnesium bromide (prepared from vinyl bromide (1 mole) and magnesium (1 g.-atom) in tetrahydrofuran) cooled in an ice bath. When the addition was complete, the reactants were allowed to stand overnight at room temperature and subsequently cooled to 0° and hydrolyzed by the addition of an ice-cold saturated solution of ammonium chloride and ammonium hydroxide. The aqueous layer was extracted several times with ether; the combined organic layer and ether extract were washed with water and dried over potassium carbonate.

The solvents were removed by distillation under atmospheric pressure and the residue fractionally distilled under reduced pressure. In this way the following fractions were obtained: (*1*) b.p. up to 82°/12.5 mm. traces of terpenoid hydrocarbons; (*2*) b.p. 83–85°/12.5 mm., (±)-linaloöl (103 g., 83% yield); (*3*) b.p. 85–95°/12.5 mm., traces. The residue (14 g.) distilled without any forerun under a pressure of 0.2 mm. and had an odor of violets.

D. 3-VINYL-2-METHYLCYCLOHEX-2-ENONE (14)

Freshly distilled 3-isobutoxy-2-methylcyclohex-2-enone (b.p. 109–110°/0.5 mm.) (0.1 mole) in tetrahydrofuran (30 ml.) was added slowly to a stirred suspension of vinylmagnesium bromide (from vinyl bromide (0.15 mole) and magnesium (0.1 g.-atom)) cooled in ice. After the addition was complete, the reactants were heated at 70–80° for 1 hr. and subsequently allowed to stand overnight at room temperature. The reaction mixture was then cooled to 0° and hydrolyzed with excess ice-cold 1*N* sulfuric acid, and the aqueous layer was extracted with ether (2 × 25 ml.). The combined ether extract and organic layer was washed with water, sodium carbonate solution (10%), and water, and finally dried over anhydrous sodium sulfate.

The carbonate extract, on acidification, gave 2-methyldihydroresorcinol (1 g., m.p. 209°) (ex alcohol).

The solvents and isobutanol were removed from the dried organic extract by distillation at the water pump. The residue on distillation

gave 3-vinyl-2-methylcyclohex-2-enone (9.5 g., 70% yield) as a pale yellow oil, b.p. 56–57°/0.6 mm., d_4^{21} 0.998, n_D^{21} 1.5519. The red 2,4-dinitrophenylhydrazone had m.p. 181° (ex alcohol).

E. PENT-2-EN-4-ONE (43)

Propenylmagnesium bromide is prepared from 1-bromopropene (0.2 mole) and magnesium (0.2 g.-atom). The Grignard reagent is siphoned, with the aid of nitrogen, into a double-surfaced Mariotte flask, tepid water being circulated in the jacket in order to prevent crystallization. The flask is connected to a three-necked flask equipped with a stirrer and reflux condenser, moisture being excluded in the usual way. In the flask is placed acetic anhydride (0.4 mole) in THF (30 ml.) cooled to −60 or −70°, and the solution of the Grignard reagent is added dropwise over a period of 2–3 hr. with vigorous stirring. The reaction mixture, after standing overnight in the refrigerating mixture, is allowed to warm up to 0° before being decomposed by an ice-cold saturated solution of ammonium chloride (75 ml.).

The aqueous layer is extracted with ether (4 × 25 ml.). The ether extracts and the organic layer are washed with sodium carbonate, filtered, and dried, in the presence of hydroquinone, over anhydrous sodium sulfate in a nitrogen atmosphere.

The solvents are removed by distillation on a water bath up to a temperature of 75°, the residue being distilled under reduced pressure and the distillate being collected in a dry ice trap. The distillate on fractionation under atmospheric pressure gave pent-2-en-4-one (13.4 g., 80% yield), b.p. 120–123°, d_4^{20} 0.857, n_D^{20} 1.4360. The 2,4-dinitrophenylhydrazone has m.p. 158° (ex alcohol).

IV. Tables of Products

TABLE IX

Organomagnesium halide	Halide	Reaction product	Yield, %	Ref.
		Vinylsilanes		
CH_2=CHMgCl	$(CH_3)_3SiCl$	$(CH_3)_3SiCH$=CH_2		74
CH_2=CHMgCl	$(CH_3)_2SiCl_2$	$(CH_3)_2Si(CH$=$CH_2)_2$	66.1	74
CH_2=CHMgCl	CH_3SiCl_3	$CH_3Si(CH$=$CH_2)_3$		74
CH_2=CHMgCl	$SiCl_4$	$Si(CH$=$CH_2)_4$	87.5	74
CH_2=CHMgCl	$C_6H_5SiCl_3$	$C_6H_5Si(CH$=$CH_2)_3$		74
CH_2=CHMgCl	$(C_6H_5)_2SiCl_2$	$(C_6H_5)_2Si(CH$=$CH_2)_2$	80	74
CH_2=CHMgCl	$(C_6H_5)_3SiCl$	$(C_6H_5)_3SiCH$=CH_2	73.5	74
CH_2=CHMgCl	$SiHCl_3$	$SiH(CH$=$CH_2)_3$		74
CH_2=CHMgCl	$(n\text{-}C_4H_9)_2SiCl_2$	$(n\text{-}C_4H_9)_2Si(CH$=$CH_2)_2$		74
		Vinyltins		
CH_2=CHMgCl	$(CH_3)_2SnCl_2$	$(CH_3)_2Sn(CH$=$CH_2)_2$	75	75
CH_2=CHMgCl	$SnCl_4$	$Sn(CH$=$CH_2)_4$	82	75
CH_2=CHMgCl	$(n\text{-}C_4H_9)_2SnCl_2$	$(n\text{-}C_4H_9)_2Sn(CH$=$CH_2)_2$	89	75
CH_2=CHMgCl	$(n\text{-}C_4H_9)_2SnO$	$(n\text{-}C_4H_9)_2Sn(CH$=$CH_2)_2$	58	75
CH_2=CHMgCl	$(n\text{-}C_4H_9)_3SnCl$	$(n\text{-}C_4H_9)_3SnCH$=CH_2	82	75
CH_2=CHMgCl	$(n\text{-}C_4H_9)_6Sn_2O$	$(n\text{-}C_4H_9)_3SnCH$=CH_2	85	75
CH_2=CHMgCl	$(C_6H_5)_2SnCl_2$	$(C_6H_5)_2Sn(CH$=$CH_2)_2$	73	75
CH_2=CHMgCl	$(C_6H_5)_3SnCl$	$(C_6H_5)_3SnCH$=CH_2	79	75
CH_2=CHMgCl	$n\text{-}C_4H_9SnCl_3$	$n\text{-}C_4H_9(CH$=$CH_2)SnCl_2$	54	75
CH_2=CHMgCl	$n\text{-}C_4H_9SnCl_3$	$n\text{-}C_4H_9(CH$=$CH_2)_2SnCl$	50	75
CH_2=CHMgCl	$(n\text{-}C_4H_9)_2SnCl_2$	$(n\text{-}C_4H_9)_2(CH$=$CH_2)SnCl$	56	75
CH_2=CHMgBr	$(CH_3)_3SnBr$	$(CH_3)_3SnCH$=CH_2	68	78

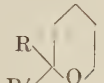
(*continued*)

TABLE IX (*continued*)

Organomagnesium halide	Halide	Reaction product	Yield, %	Ref.
CH_2=CHMgBr	$(CH_3)_2SnCl_2$	$(CH_3)_2Sn(CH=CH_2)_2$	79	78
CH_2=CHMgBr	$CH_3(C_2H_5)_2SnBr$	$CH_3(C_2H_5)_2SnCH=CH_2$	77	78
CH_2=CHMgBr	$SnCl_4$	$Sn(CH=CH_2)_4$	74	78
CH_2=CHMgBr	$(C_2H_5)_3SnBr$	$(C_2H_5)_3SnCH=CH_2$	85	78
CH_2=CHMgBr	n-$C_4H_9SnCl_3$	n-$C_4H_9Sn(CH=CH_2)_3$	84	78
CH_2=CHMgBr	$C_6H_5SnCl_3$	$C_6H_5Sn(CH=CH_2)_3$	38	78
CH_2=CHMgBr	$(n$-$C_4H_9)_2SnCl_2$	$(n$-$C_4H_9)_2Sn(CH=CH_2)_2$	85	78
CH_2=CHMgBr	$(n$-$C_4H_9)_3SnCl$	$(n$-$C_4H_9)_3SnCH=CH_2$	85	
CH_2=CHMgBr	$(C_6H_5)_2SnCl_2$	$(C_6H_5)_2Sn(CH=CH_2)_2$	68	79
CH_2=CHMgBr	$(C_6H_5)_3SnCl$	$(C_6H_5)_3SnCH=CH_2$	82	78
CH_2=CHMgBr	$((CH_3)_3SiCH_2)_2SnBr_2$	$((CH_3)_3SiCH_2)_2Sn(CH=CH_2)_2$	79.5	83
		Vinylgermanes		
CH_2=CHMgBr	$(C_2H_5)_2GeCl_2$	$(C_2H_5)_2Ge(CH=CH_2)_2$	70	82
CH_2=CHMgBr	$GeCl_4$	$Ge(CH=CH_2)_4$ +	35.4	82
		$(CH_2=CH)_3GeGe(CH=CH_2)_3$	26.1	82
CH_2=CHMgBr	$C_2H_5GeCl_3$	$C_2H_5Ge(CH=CH_2)_3$	50	82
		Vinyl Derivatives of Group V Elements		
CH_2=CHMgBr	PCl_3	$(CH=CH)_3P$	18	41
CH_2=CHMgBr	$C_6H_5PCl_2$	$C_6H_5P(CH=CH_2)_2$		41
CH_2=CHMgBr	$AsCl_3$	$(CH_2=CH)_3As$	62	41
CH_2=CHMgBr	$SbCl_3$	$(CH_2=CH)_3Sb$	66	41
CH_2=CHMgBr	$BiCl_3$	$(CH_2=CH)_3Bi$	28	41

TABLE X-A

Action of Alkenylmagnesium Halides on α-Halogeno Ethers

Organomagnesium halide	α-Halogeno ether	Reaction product	Yield, %	Ref.
CH_2=CHMgBr	n-$C_4H_9OCH_2Cl$	CH_2=$CHCH_2OC_4H_9$	67	51
CH_2=CHMgBr	n-$C_6H_{13}CH(OC_2H_5)Cl$	CH_2=$CHCH(OC_2H_5)C_6H_{13}$	50[a]	51
		R / R′		
CH_2=CHMgBr	2-Bromotetrahydrofuran	H / CH_2=CH—	55	18
CH_2=CHMgBr	2-Chlorotetrahydrofuran	H / CH_2=CH—	67	18
CH_3CH=CHMgBr	2-Chloro-2-methyltetrahydrofuran	Me / CH_3CH=CH—	52	18
				
		R / R′		
CH_2=CHMgBr	2-Bromotetrahydropyran	H / CH_2=CH—	68	18
CH_3CH=CHMgBr	2-Bromotetrahydropyran	H / CH_3CH=CH—	70	18
$(CH_3)_2C$=CHMgBr	2-Bromotetrahydropyran	H / $(CH_3)_2CH$=CH—	62	18
CH_3CH=CHMgBr	2-Chloro-2-methyltetrahydropyran	Me / CH_3CH=CH—	65	18

[a] Yield based on n-$C_6H_{13}CHO$.

TABLE X-B
Action of Alkenylmagnesium Halides on α,β-Dihalogeno Ethers

Organomagnesium halide (RMgX)	α,β-Dihalogeno ether	Reaction product	Yield, %	Ref.
$CH_2{=}CHMgBr$	$C_2H_5OCHClCH_2Cl$	$RCH(OC_2H_5)CH_2Cl$	65	63
$CH_2{=}CHMgBr$	$C_2H_5OCHBrCH_2Br$	$RCH(OC_2H_5)CH_2Br$	58	63
$CH_2{=}CHMgBr$	$C_2H_5OCHBrCHBrCH_3$	$RCH(OC_2H_5)CHBrCH_3$	55	63
$CH_2{=}CHMgBr$	$C_2H_5OCHBrCHBrC_2H_5$	$RCH(OC_2H_5)CHBrC_2H_5$	60	63
$CH_2{=}CHMgBr$	$C_2H_5OCHBrCHBr(n\text{-}C_5H_{11})$	$RCH(OC_2H_5)CHBr(n\text{-}C_5H_{11})$	60	63
$CH_2{=}C(CH_3)MgBr$	$C_2H_5OCHClCH_2Cl$	$RCH(OC_2H_5)CH_2Cl$	50	63
$CH_2{=}C(CH_3)MgBr$	$C_2H_5OCHBrCH_2Br$	$RCH(OC_2H_5)CH_2Br$	70	63
$CH_2{=}C(CH_3)MgBr$	$C_2H_5OCHBrCHBrC_2H_5$	$RCH(OC_2H_5)CHBrC_2H_5$	52	63
$CH_3CH{=}CHMgBr$	$C_2H_5OCHClCH_2Cl$	$RCH(OC_2H_5)CH_2Cl$	70	63
$CH_3CH{=}CHMgBr$	$C_2H_5OCHBrCH_2Br$	$RCH(OC_2H_5)CH_2Br$	70	50
$CH_3CH{=}CHMgBr$	$C_2H_5OCHBrCHBrCH_3$	$RCH(OC_2H_5)CHBrCH_3$	65	50
$CH_3CH{=}CHMgBr$	$C_2H_5OCHBrCHBrC_2H_5$	$RCH(OC_2H_5)CHBrC_2H_5$	65	50
$CH_3CH{=}CHMgBr$	$C_2H_5OCHBrCHBr(n\text{-}C_5H_{11})$	$RCH(OC_2H_5)CHBr(n\text{-}C_5H_{11})$	55	63
$(CH_3)_2C{=}CHMgBr$	$C_2H_5OCHClCH_2Cl$	$RCH(OC_2H_5)CH_2Cl$	75	63
$(CH_3)_2C{=}CHMgBr$	$C_2H_5OCHBrCHBrCH_3$	$RCH(OC_2H_5)CHBrCH_3$	67	63
$(CH_3)_2C{=}CHMgBr$	$C_2H_5OCHBrCHBrC_2H_5$	$RCH(OC_2H_5)CHBrC_2H_5$	50	63
$(CH_3)_2C{=}CHMgBr$	$C_2H_5OCHBrCHBr(n\text{-}C_5H_{11})$	$RCH(OC_2H_5)CHBr(n\text{-}C_5H_{11})$	45	63
$C_6H_5C(CH_3){=}CHMgBr$	$C_2H_5OCHClCH_2Cl$	$RCH(OC_2H_5)CH_2Cl$	70	63
$C_6H_5C(CH_3){=}CHMgBr$	$C_2H_5OCHBrCH_2Br$	$RCH(OC_2H_5)CH_2Br$	70	63
$C_6H_5C(CH_3){=}CHMgBr$	$C_2H_5OCHBrCHBrC_2H_5$	$RCH(OC_2H_5)CHBrC_2H_5$	56	63
$C_6H_5C(CH_3){=}CHMgBr$	$C_2H_5OCHBrCHBr(n\text{-}C_5H_{11})$	$RCH(OC_2H_5)CHBr(n\text{-}C_5H_{11})$	40	63

TABLE X-C

α,β-Unsaturated Ketones Prepared from Alkenylmagnesium Halides

Organomagnesium halide	Ketone prepared	Yield, %		Ref.
		From α,β-dihalogeno ether	From imino chloride	
CH_2=$CHMgBr$	CH_3COCH=CH_2	36		63
CH_3CH=$CHMgBr$	CH_3COCH=$CHCH_3$	63	50	63
CH_3CH=$CHMgBr$	C_2H_5COCH=$CHCH_3$	45	45	63
CH_3CH=$CHMgBr$	n-C_3H_7COCH=$CHCH_3$	40		63
$(CH_3)_2C$=$CHMgBr$	iso-C_3H_7COCH=$CHCH_3$		50	63
CH_3CH=$CHMgBr$	n-C_3H_7COCH=$C(CH_3)_2$	48		63
CH_3CH=$CHMgBr$	C_6H_5COCH=$CHCH_3$		45	63
$C_6H_5C(CH_3)$=$CHMgBr$	n-$C_6H_{13}COCH$=$CHCH_3$	48		63
$C_6H_5C(CH_3)$=$CHMgBr$	CH_3COCH=$C(C_6H_5)CH_3$	60		63
	C_2H_5COCH=$C(C_6H_5)CH_3$	46		63

TABLE X-D
Ethylenic Alcohols Prepared from 2-Halogen Oxiranes

Organomagnesium halide	Intermediate (A)	Alcohol	Yield from A, %	Ref.
$CH_2{=}CHMgBr$	$C_4H_7OCHBrCH_3$	$CH_3CH{=}CH(CH_2)_3OH$	88	18
$CH_3CH{=}CHMgBr$	$C_4H_7OCHBrC_2H_5$	$C_2H_5CH{=}CH(CH_2)_3OH$	81	18
$CH_3CH{=}CHMgBr$	$C_4H_6O(CH_3)CHBrC_2H_5$	$C_2H_5CH{-}C(CH_3)(CH_2)_3OH$	48	18
$CH_2{=}CHMgBr$	$C_5H_9OCHBrCH_3$	$CH_3CH{=}CH(CH_2)_4OH$	85	18
$CH_3CH{=}CHMgBr$	$C_5H_9OCHBrC_2H_5$	$C_2H_5CH{=}CH(CH_2)_4OH$	82	18
$(CH_3)_2C{=}CHMgBr$	$C_5H_9OCHBr(iso\text{-}C_3H_7)$	$iso\text{-}C_3H_7CH{-}CH(CH_2)_4OH$	60	18
$CH_3CH{=}CHMgBr$	$C_5H_9O(CH_3)CHBrC_2H_5$	$C_2H_5CH{-}C(CH_3)(CH_2)_4OH$	55	18
$CH_3CH{=}CHMgBr$	$(C_4H_6OCl)CH{=}CHCH_3$	$CH_3CH{=}CHCH{=}CH(CH_2)_2OH$		54
$CH_3CH{=}CHMgBr$	$(C_5H_8OCl)CH{-}CHCH_3$	$CH_3CH{=}CHCH{=}CH(CH_2)_3OH$		54

TABLE X-E
1,4-Dienes

Organomagnesium halide	Halogeno compound	Product	Yield, %	Ref.
CH_2=CHMgBr	$BrCH_2CH$=CH_2	CH_2=$CHCH_2CH$=CH_2	73	50
CH_2=CHMgBr	$ClCH_2C(CH_3)$=CH_2	CH_2=$CHCH_2C(CH_3)$=CH_2	62	50
CH_2=CHMgBr	$BrCH_2C(Br)$=CH_2	CH_2=$CHCH_2C(Br)$=CH_2	58	50
CH_3CH=CHMgBr	$BrCH_2CH$=CH_2	CH_3CH=$CHCH_2CH$=CH_2	80	50
CH_2=CHMgBr	C_2H_5CH=$CHCH_2Br$	Mixture of dienes	80	50
CH_3CH=CHMgBr	$ClCH_2CH$=$CHCH_2OH$	CH_3CH=$CHCH_2CH$=$CHCH_2OH$	71	54

TABLE XI-A
Ethylenic Acetals

Organomagnesium halide	Acetal	Yield, %	M.p. of 2,4-DNP, °C.	Ref.
$CH_2{=}C(n\text{-}C_5H_{11})MgX$	$CH_2{=}C(n\text{-}C_5H_{11})CH(OC_2H_5)_2$	50	125–126	55
$CH_2{=}C(C_6H_5)MgX$	$CH_2{=}C(C_6H_5)CH(OC_2H_5)_2$	50	265	55
$CH_2{=}C(CH_2C_6H_5)MgX$	$CH_2{=}C(CH_2C_6H_5)CH(OC_2H_5)_2$	50	178–179	55

TABLE XI-B
β-Ethylenic Alcohols

Organomagnesium halide	Epoxide	Product	Yield, %	Ref.
$CH_2{=}CHMgBr$	Ethylene oxide	$CH_2{=}CHCH_2CH_2OH$	65	52
$(CH_3)_2C{=}CHMgBr$	Ethylene oxide	$(CH_3)_2C{=}CHCH_2CH_2OH$	70	52
$C_6H_5CH{=}CHMgBr$	Ethylene oxide	$C_6H_5CH{=}CHCH_2CH_2OH$	Low	52
$CH_3CH{=}CHMgBr$	Propylene oxide	$CH_3CH{=}CHCH_2CH(OH)CH_3$	60	52

TABLE XI-C
Ethylenic Amines

Organomagnesium halide	OC_4H_9 / RCH / NR'_2 R	R′	Product	Yield, %	Ref.
$CH_2{=}CHMgBr$	H	C_2H_5	$CH_2{=}CHCH_2N(C_2H_5)_2$		19
$CH_2{=}CHMgBr$	C_6H_5	C_4H_8[a]	$CH_2{=}CHCH(C_6H_5)NC_4H_8$	60	19
$CH_3CH{=}CHMgBr$	H	C_2H_5	$CH_3CH{=}CHCH_2N(C_2H_5)_2$	90	19
$CH_3CH{=}CHMgBr$	H	C_4H_8[a]	$CH_3CH{=}CHCH_2NC_4H_8$	75	19
$CH_3CH{=}CHMgBr$	C_6H_5	CH_3	$CH_3CH{=}CHCH(C_6H_5)N(CH_3)_2$	93	19
$CH_3CH{=}CHMgBr$	C_6H_5	C_4H_8[a]	$CH_3CH{=}CHCH(C_6H_5)NC_4H_8$	94	19
$CH_3CH{=}CHMgBr$		C_2H_5	$CH_3CH{=}CHCH(C_6H_5)N(C_2H_5)_2$	73	19
$(CH_3)_2C{=}CHMgBr$	H	C_4H_8[a]	$(CH_3)_2C{=}CHCH_2NC_4H_8$	70	19
$(CH_3)_2C{=}CHMgBr$	C_6H_5	C_2H_5	$(CH_3)_2C{=}CHCH(C_6H_5)N(C_2H_5)_2$	87	19
$C_6H_5C(CH_3){=}CHMgBr$	H	C_4H_8[a]	$C_6H_5C(CH_3){=}CHCH_2NC_4H_8$	70	19

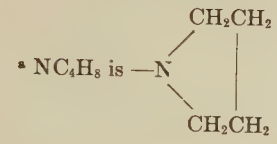
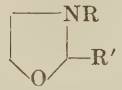
[a] NC_4H_8 is 

TABLE XI-D
Ethylenic Amino Alcohols

Organomagnesium halide	Amino ether		Product	Yield, %	Ref.
CH_2=CHMgBr	$C_5H_9ON(C_2H_5)_2$[a]		CH_2=CHCH(CH_2)$_3CH_2OH$ $N(C_2H_5)_2$	50	19
CH_3CH=CHMgBr	$C_5H_9ON(C_2H_5)_2$[a]		CH_3CH=CHCH(CH_2)$_3CH_2OH$ $N(C_2H_5)_2$	70	19
CH_3CH=CHMgBr	$CH_2(CH_2)_2N(n\text{-}C_4H_9)$ $O—CHC_6H_5$		CH_3CH=CHCH(C_6H_5)N(n-C_4H_9)$CH_2CH_2CH_2OH$	80	19
					
	R	R′			
CH_3CH=CHMgBr	CH_3	H	CH_3CH=CHCH_2N(CH_3)CH_2CH_2OH	48	19
CH_3CH=CHMgBr	C_6H_5	H	CH_3CH=CHCH_2N(C_6H_5)CH_2CH_2OH	68	19
CH_3CH=CHMgBr	CH_3	C_6H_5	CH_3CH=CHCH(C_6H_5)N(CH_3)CH_2CH_2OH	72	19
CH_3CH=CHMgBr	C_6H_5	CH_3	CH_3CH=CHCH(CH_3)N(C_6H_5)CH_2CH_2OH	69	19

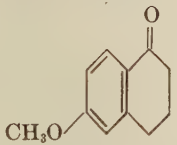
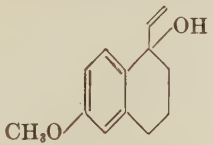
[a] C_5H_9O is

TABLE XII-A

α-Ethylenic Secondary Alcohols

Organomagnesium halide	Aldehyde	Product	Yield, %	Ref.
CH_2=CHMgBr	$(CH_2O)_3$	CH_2=CHCH$_2$OH	50	51
CH_2=CHMgBr	*n*-C_3H_7CHO	CH_2=CHCH(OH)(*n*-C_3H_7)	85	51
CH_2=CHMgBr	C_6H_5CHO	CH_2=CHCH(OH)C_6H_5	67	51
CH_2=CHMgBr	*n*-$C_6H_{13}CHO$	CH_2=CHCH(OH)(*n*-C_6H_{13})	67	42
CH_3CH=CHMgBr	*n*-C_3H_7CHO	CH_3CH=CHCH(OH)(*n*-C_3H_7)	60	51
CH_3CH=CHMgBr	*n*-$C_6H_{13}CHO$	CH_3CH=CHCH(OH)(*n*-C_6H_{13})	64	51
CH_3CH=CHMgBr	*n*-$C_6H_{13}CHO$	CH_3CH=CHCH(OH)(*n*-C_6H_{13})	77	42
CH_3CH=CHMgBr	*n*-$C_7H_{15}CHO$	CH_3CH=CHCH(OH)(*n*-C_7H_{15})	64	51
CH_3CH=CHMgBr	*n*-$C_9H_{19}CHO$	CH_3CH=CHCH(OH)(*n*-C_9H_{19})	76	51
CH_2=C(CH_3)MgBr	CH_3CHO	CH_2=C(CH_3)CH(OH)CH_3	83	39
CH_2=C(CH_3)MgBr	*n*-C_3H_7CHO	CH_2=C(CH_3)CH(OH)(*n*-C_3H_7)	66	39
CH_2=C(CH_3)MgBr	C_6H_5CHO	CH_2=C(CH_3)CH(OH)C_6H_5	80	39
CH_2=C(CH_3)MgBr	*n*-$C_6H_{13}CHO$	CH_2=C(CH_3)CH(OH)(*n*-C_6H_{13})	79	39
CH_2=C(CH_3)MgBr	*p*-(*i*-C_3H_7)C_6H_4CHO	CH_2=C(CH_3)CH(OH)C_6H_4(iso-C_3H_7)*p*	80	39
cis-CH_3CH=C(CH_3)MgBr	CH_3CHO	*cis*-CH_3CH=C(CH_3)CH(OH)CH_3	80	60
trans-CH_3CH=C(CH_3)MgBr	CH_3CHO	*trans*-CH_3CH=C(CH_3)CH(OH)CH_3		
$(CH_3)_2$C=CHMgBr	CH_2O	$(CH_3)_2$C=CHCH$_2$OH	43	51
$(CH_3)_2$C=CHMgBr	CH_3CHO	$(CH_3)_2$C=CHCH(OH)CH_3	81	39
$(CH_3)_2$C=CHMgBr	$C_6H_{13}CHO$	$(CH_3)_2$C=CHCH(OH)C_6H_{13}	64	51
$C_6H_5C(CH_3)$=CHMgBr	CH_3CHO	$C_6H_5C(CH_3)$=CHCH(OH)CH_3	81	39
$(C_6H_5)_2$C=CHMgBr	CH_3CHO	$(C_6H_5)_2$C=CHCH(OH)CH_3	50	39

TABLE XII-B
α-Ethylenic *tert*-Alcohols

Organomagnesium halide	Ketone	Product	Yield, %	Ref.
$CH_2{=}CHMgBr$	CH_3COCH_3	$(CH_3)_2C(OH)CH{=}CH_2$	74	51
$CH_2{=}CHMgCl$	CH_3COCH_3	$(CH_3)_2C(OH)CH{=}CH_2$	74	65
$CH_2{=}CHMgCl$			86	46
$CH_3CH{=}CHMgBr$	CH_3COCH_3	$(CH_3)_2C(OH)CH{=}CHCH_3$	75	51
$CH_3CH{=}CHMgBr$	$CH_3CO(n\text{-}C_5H_{11})$	$(CH_3)(C_5H_{11})C(OH)CH{=}CHCH_3$	77	39
$CH_3CH{=}CHMgBr$	$C_2H_5CO(n\text{-}C_4H_9)$	$(C_2H_5)(C_4H_9)C(OH)CH{=}CHCH_3$	83	39
$CH_3CH{=}CHMgBr$	$(n\text{-}C_3H_7)_2CO$	$(C_3H_7)_2C(OH)CH{=}CHCH_3$	78	59
$CH_3CH{=}CHMgBr$	$CH_3COC_6H_5$	$CH_3(C_6H_5)C(OH)CH{=}CHCH_3$	80	38
$CH_3CH{=}CHMgBr$	$CH_3CO(n\text{-}C_7H_{15})$	$(CH_3)(C_7H_{15})C(OH)CH{=}CHCH_3$	70	51
$CH_3CH{=}CHMgBr$	$CH_3CO(n\text{-}C_9H_{19})$	$(CH_3)(C_9H_{19})C(OH)CH{=}CHCH_3$	68	51
$CH_3CH{=}CHMgBr$	$C_6H_5COC_6H_5$	$(C_6H_5)_2C(OH)CH{=}CHCH_3$	40	59
$CH_2{=}C(CH_3)MgBr$	CH_3COCH_3	$(CH_3)_2C(OH)C(CH_3){=}CH_2$	56	39

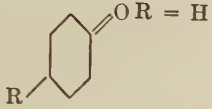
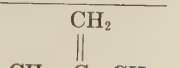
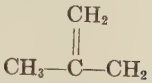
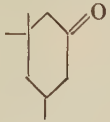
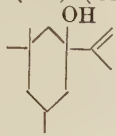
$CH_2{=}C(CH_3)MgBr$	CH_2COCH_3	$(CH_3)_2C(OH)C(CH_3){=}CH_2$	56	39
$CH_2{=}C(CH_3)MgBr$	 R = H	H 	40	59
$CH_2C(CH_3MgBr$	R = CH_3	CH_3 		
$CH_2{=}C(CH_3)MgBr$	$CH_3CO(n\text{-}C_5H_{11})$	$(CH_3)(C_5H_{11})C(OH)C(CH_3){=}CH_2$	70	39
$CH_2{=}C(CH_3)MgBr$	$C_2H_5CO(n\text{-}C_4H_9)$	$(C_2H_5)(C_4H_9)C(OH)C(CH_3){=}CH_2$	55	39
$CH_2{=}C(CH_3)MgBr$	$CH_3COC_6H_5$	$(CH_3)(C_6H_5)C(OH)C(CH_3){=}CH_2$	65	39
$CH_2C(CH_3MgBr$			56	59

TABLE XII-C
Trichloromethylvinyl Carbinols

Organomagnesium halide	Aldehyde	Product	Yield, %	Ref.
$CH_2{=}CHMgBr$	CCl_3CHO	$CH_2{=}CHCH(OH)CCl_3$	84	58
$CH_3CH{=}CHMgBr$	CCl_3CHO	$CH_3CH{=}CHCH(OH)CCl_3$	87	58
$CH_2{=}C(CH_3)MgBr$	CCl_3CHO	$CH_2{=}C(CH_3)CH(OH)CCl_3$	70	58
$CH_3CH{=}C(CH_3)MgBr$	CCl_3CHO	$CH_3CH{=}C(CH_3)CH(OH)CCl_3$	73	58
$(CH_3)_2C{=}CHMgBr$	CCl_3CHO	$(CH_3)_2C{=}CHCH(OH)CCl_3$	90	58
$(CH_3)_2C{=}C(CH_3)MgBr$	CCl_3CHO	$(CH_3)_2C{=}C(CH_3)CH(OH)CCl_3$	50	58

TABLE XII-D
Ethylenic Amino Alcohols

Organomagnesium halide	Carbonyl compound	Product	Yield, %	Ref.
	$Et_2NCHRCHO$			
$CH_2{=}CHMgBr$	R = C_2H_5	$CH_2{=}CHCH(OH)CH(C_2H_5)NEt_2$	93	56
$CH_2{=}CHMgBr$	R = n-C_5H_{11}	$CH_2{=}CHCH(OH)CH(C_5H_{11})NEt_2$	70	56
$CH_3CH{=}CHMgBr$	R = C_2H_5	$CH_3CH{=}CHCH(OH)CH(C_2H_5)NEt_2$	61	56
$CH_3CH{=}CHMgBr$	R = n-C_5H_{11}	$CH_3CH{=}CHCH(OH)CH(C_5H_{11})NEt_2$	73	56
	$CH_3COCH(R)NEt_2$			
$CH_2{=}CHMgBr$	R = H	$CH_2{=}CHC(CH_3)(OH)CH_2NEt_2$	68	56
$CH_2{=}CHMgBr$	R = CH_3	$CH_2{=}CHC(CH_3)(OH)CH(CH_3)NEt_2$	80	56
$CH_3CH{=}CHMgBr$	R = H	$CH_3CH{=}CHC(CH_3)(OH)CH_2NEt_2$	70	56
$CH_3CH{=}CHMgBr$	R = CH_3	$CH_3CH{=}CHC(CH_3)(OH)CH(CH_3)NEt_2$	72	56
$CH_2{=}CHMgBr$	$Et_2NCH_2CH(C_2H_5)CHO$	$CH_2{=}CHCH(OH)CH(C_2H_5)CH_2NEt_2$	74	56
$CH_3CH{=}CHMgBr$	$Et_2NCH_2CH(C_2H_5)CHO$	$CH_3CH{=}CHCH(OH)CH(C_2H_5)CH_2NEt_2$	73	56
	$CH_3COCH(R)CH_2NEt_2$			
$CH_2{=}CHMgBr$	R = H	$CH_2{=}CHC(CH_3)(OH)CH_2CH_2NEt_2$	51	56
$CH_2{=}CHMgBr$	R = CH_3	$CH_2{=}CHC(CH_3)(OH)CH(CH_3)CH_2NEt_2$	70	56
$CH_3CH{=}CHMgBr$	R = H	$CH_3CH{=}CHC(CH_3)(OH)CH_2CH_2NEt_2$	50	56
$CH_3CH{=}CHMgBr$	R = CH_3	$CH_3CH{=}CHC(CH_3)(OH)CH(CH_3)CH_2NEt_2$	70	56

TABLE XII-E
α,α'-Diethylenic Alcohols

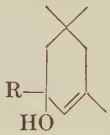
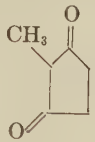
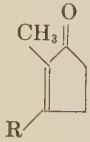
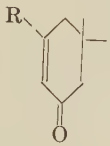
Organomagnesium halide	Carbonyl compound	Product	Yield, %	Ref.
$CH_2{=}CHMgBr$	$CH_2{=}CHCHO$	$CH_2{=}CHCH(OH)CH{=}CH_2$	50	2
$CH_2{=}CHMgBr$	$CH_3CH{=}CHCHO$	$CH_2{=}CHCH(OH)CH{=}CHCH_3$	58	54
$CH_2{=}CHMgBr$	$CH_3CH{=}CHCHO$	$CH_2{=}CHCH(OH)CH{=}CHCH_3$	63	2
$CH_2{=}C(CH_3)MgBr$	$CH_3CH{=}CHCHO$	$CH_2{=}C(CH_3)CH(OH)CH{=}CHCH_3$	42	39
$CH_3CH{=}C(CH_3)MgBr$	$CH_2{=}CHCHO$	$CH_2{=}CHCH(OH)C(CH_3){=}CHCH_3$	48	42
$CH_2{=}CHMgBr$	$CH_3COCH{=}CCl_2$	$CH_2{=}CHC(CH_3)(OH)CH{=}CCl_2$	80	31
$CH_2{=}CHMgBr$	$CH_3COCH{=}C(CH_3)_2$	$CH_2{=}CHC(CH_3)(OH)CH{=}C(CH_3)_2$	60	54
$CH_2{=}CHMgBr$	Isophorone	 R = $CH_2{=}CH{-}$	70	59
$CH_3CH{=}CHMgBr$	Isophorone	R = $CH_3CH{=}CH{-}$	50	59
$CH_2{=}C(CH_3)MgBr$	$CH_3COCH{=}C(CH_3)_2$	$CH_2{=}C(CH_3)C(CH_3)(OH)CH{=}C(CH_3)_2$	50	39
$CH_3CH{=}CHMgBr$	$CH_3COCH{=}CHCl$	$CH_3CH{=}CHC(CH_3)(OH)CH{=}CHCl$		66
$(CH_3)_2C{=}CHMgBr$	$CH_3COCH{=}CCl_2$	$(CH_3)_2C{=}CHC(CH_3)(OH)CH{=}CCl_2$		31
$(CH_3)_2C{=}CHMgBr$	$((CH_3)_2C{=}CH)_2CO$	$((CH_3)_2C{=}CH)_3COH$	50	59

TABLE XII-F
Conjugated Dienones

Organomagnesium halide	β-Diketone	Product	Yield, %	Ref.
CH_2=CHMgX	$CH_3COCH_2COCH_3$	CH_2=$CHC(CH_3)$=$CHCOCH_3$	46	14
CH_3CH=CHMgX	$CH_3COCH_2COCH_3$	CH_3CH=$CHC(CH_3)$=$CHCOCH_3$	70	14
$(CH_3)_2C$=CHMgX	$CH_3COCH_2COCH_3$	$(CH_3)_2C$=$CHC(CH_3)$=$CHCOCH_3$		14
$C_6H_5C(CH_3)$=CHMgX	$CH_3COCH_2COCH_3$	$C_6H_5C(CH_3)$=$CHC(CH_3)$=$CHCOCH_3$	70	14
CH_2=CHMgX		 R = CH_2=CH—	35	14
CH_3CH=CHMgX		R = CH_3CH=CH—	50	14
$(CH_3)_2C$=CHMgX		R = $(CH_3)_2C$=CH—	72	14
$(C_6H_5)C(CH_3)$=CHMgX		R = $(C_6H_5)C(CH_3)$=CH—	60	14
CH_2=CHMgX	Dimedone	 R = CH_2=CH—	72	14
CH_3CH=CHMgX	Dimedone	R = CH_3CH=CH—	65	14
$(CH_3)_2C$=CHMgX	Dimedone	R = $(CH_3)_2C$=CH—	85	14

(*continued*)

TABLE XII-F (*continued*)

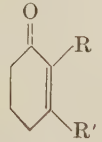
Organomagnesium halide	β-Diketone	Product		Yield, %	Ref.
					
		R	R′		
CH_2=CHMgX	2-Methyldihydroresorcinol	Me	CH_2=CH—	70	14
CH_2=CHMgX	2-Methyldihydroresorcinol	Me	CH_2=CH—	70	46
CH_2=CHMgX	Dihydroresorcinol	H	CH_2=CH—	90	14
CH_3CH=CHMgX	Dihydroresorcinol	H	CH_3CH=CH—	74	14
$(CH_3)_2C$=CHMgX	Dihydroresorcinol	H	$(CH_3)_2C$=CH—	86	14
$C_6H_5C(CH_3)$=CHMgX	Dihydroresorcinol	H	$C_6H_5C(CH_3)$=CH—	94	14

TABLE XIII-A
Diethylenic Alcohols

Organomagnesium halide	Ester	Product	Yield, %	Ref.
CH_2=CHMgBr	$HCOOC_2H_5$	CH_2=CHCH(OH)CH=CH_2	60	54
CH_2=CHMgBr	$CH_3COOC_2H_5$	$CH_3C(OH)(CH=CH_2)_2$	85	42
CH_2=CHMgCl	$CH_3COOC_2H_5$	$CH_3C(OH)(CH=CH_2)_2$	44	39
CH_2=CHMgBr	$C_2H_5COOC_2H_5$	$C_2H_5C(OH)(CH=CH_2)_2$	58	39
CH_2=CHMgBr	n-$C_3H_7COOC_2H_5$	n-$C_3H_7C(OH)(CH=CH_2)_2$	49	39
CH_2=CHMgCl	n-$C_3H_7COOC_2H_5$	n-$C_3H_7C(OH)(CH=CH_2)_2$	66	39
CH_2=CHMgBr	$C_6H_5COOC_2H_5$	$C_6H_5C(OH)(CH=CH_2)_2$	45	59
CH_3CH=CHMgBr	$HCOOC_2H_5$	CH_3CH=CHCH(OH)CH=$CHCH_3$	87	39
CH_3CH=CHMgBr	$CH_3COOC_2H_5$	$CH_3C(OH)(CH=CHCH_3)_2$	49	39
CH_3CH=CHMgBr	$C_2H_5COOC_2H_5$	$C_2H_5C(OH)(CH=CHCH_3)_2$	84	54
CH_3CH=CHMgBr	n-$C_3H_7COOC_2H_5$	$C_3H_7C(OH)(CH=CHCH_3)_2$	79	59
CH_3CH=CHMgBr	$C_6H_5COOC_2H_5$	$C_6H_5C(OH)(CH=CHCH_3)_2$	85	59
CH_2=C(CH_3)MgBr	$CH_3COOC_2H_5$	$CH_3C(OH)(C(CH_3)=CH_2)_2$	77	42
CH_2=C(CH_3)MgBr	iso-$C_3H_7COOC_2H_5$	iso-$C_3H_7C(OH)(C(CH_3)=CH_2)_2$	76	42

TABLE XIII-B
Triethylenic Alcohols

Organomagnesium halide	Ester	Product	Yield, %	Ref.
CH_2=$CHMgBr$	$(CH_3)_2C$=$CHCOOC_2H_5$	$(CH_2$=$CH)_2C(OH)CH$=$C(CH_3)_2$	30	59
CH_2=$CHMgBr$	C_4H_3OCH=$CHCOOC_2H_5$[a]	$(CH_2$=$CH)_2C(OH)CH$=CHC_4H_3O	20	59
CH_3CH=$CHMgBr$	$CO(OC_2H_5)_2$	$(CH_3CH$=$CH)_3COH$	30	59
CH_3CH=$CHMgBr$	CH_3CH=$CHCOOC_2H_5$	$(CH_3CH$=$CH)_3COH$	30	59
CH_3CH=$CHMgBr$	$(CH_3)_2C$=$CHCOOC_2H_5$	$(CH_3CH$=$CH)_2C(OH)CH$=$C(CH_3)_2$	70	59
CH_3CH=$CHMgBr$	CH_3CH=$CHCH$=$CHCOOC_2H_5$	$(CH_3CH$=$CH)_2C(OH)CH$=$CHCH$=$CHCH_3$		
CH_3CH=$CHMgBr$	C_6H_5CH=$CHCOOC_2H_5$	$(CH_3CH$=$CH)_2C(OH)CH$=CHC_6H_5	55	59
CH_3CH=$CHMgBr$	C_4H_3OCH=$CHCOOC_2H_5$[a]	$(CH_3CH$=$CH)_2C(OH)CH$=CHC_4H_3O	60	59
$(CH_3)_2C$=$CHMgBr$	$(CH_3)_2C$=$CHCOOC_2H_5$	$((CH_3)_2C$=$CH)_3COH$	45	59

[a] C_4H_3O =

TABLE XIII-C
α-Ethylenic Ketones

Organomagnesium halide	Anhydride	Product	Yield, %	Ref.
CH_2=CHMgCl	$(C_2H_5CO)_2O$	CH_2=CHCOC_2H_5	60	44
CH_3CH=CHMgBr	$(CH_3CO)_2O$	CH_3CH=CHCOCH_3	80	43
CH_3CH=CHMgBr	$(C_2H_5CO)_2O$	CH_3CH=CHCOC_2H_5	68	44
CH_3CH=CHMgBr	(iso-$C_3H_7CO)_2O$	CH_3CH=CHCO(iso-C_3H_7)	60	44
CH_3CH=CHMgBr	$(C_6H_5CO)_2O$	CH_3CH=CHCOC_6H_5	48	44
CH_3CH=CHMgBr	(n-$C_6H_{13}CO)_2O$	CH_3CH=CHCO(n-C_6H_{13})	70	43
CH_2=C(CH_3)MgBr	$(CH_3CH$=$CHCO)_2O$	CH_3CH=CHCOCH=$CHCH_3$	48	43
CH_2=C(CH_3)MgBr	$(CH_3CO)_2O$	CH_2=C(CH_3)$COCH_3$	50	44
$(CH_3)_2C$=CHMgBr	(n-$C_3H_7CO)_2O$	CH_2=C(CH_3)CO(n-C_3H_7)	66	43
CH_3CH=C(CH_3)MgBr	$(CH_3CH$=$CHCO)_2O$	$(CH_3)_2C$=CHCOCH=$CHCH_3$	45	44
$(CH_3)_2C$=C(CH_3)MgBr	$(CH_3CO)_2O$	CH_3CH=C(CH_3)$COCH_3$	70	44
$C_6H_5C(CH_3)$=CHMgBr	$(CH_3CO)_2O$	$(CH_3)_2C$=C(CH_3)$COCH_3$	55	44
$C_6H_5C(CH_3)$=CHMgBr	$(C_6H_5CO)_2O$	$C_6H_5C(CH_3)$=CHCOCH_3	60	43
		$C_6H_5C(CH_3)$=CHCOC_6H_5	58	43

TABLE XIII-D
α-Ethylenic Acids

Organomagnesium halide	Product	Yield,[a] %	Ref.
CH_2=CHMgBr	CH_2=CHCOOH	47	57
CH_2=C(CH_3)MgBr	CH_2=C(CH_3)COOH	50	57
CH_2=C(*n*-C_5H_{11})MgBr	CH_2=C(C_5H_{11})COOH	50	57
CH_2=C(C_6H_5)MgBr	CH_2=C(C_6H_5)COOH	66	57
CH_2=C($CH_2C_6H_5$)MgBr	CH_2=C($CH_2C_6H_5$)COOH	40	57
CH_3CH=CHMgBr	CH_3CH=CHCOOH (*cis* + *trans*)	63	57
n-$C_6H_{13}CH$=CHMgBr (*cis*)	$C_6H_{13}CH$=CHCOOH (*cis*)		42
CH_3CH=C(CH_3)MgBr	CH_3CH=C(CH_3)COOH (*cis* + *trans*)	80	57
$(CH_3)_2C$=CHMgBr	$(CH_3)_2C$=CHCOOH	50	57
$(CH_3)_2C$=C(CH_3)MgBr	$(CH_3)_2C$=C(CH_3)COOH	29	57
$C_6H_5C(CH_3)$=CHMgBr	$C_6H_5C(CH_3)$=CHCOOH		57
Camphenemagnesium bromide	Camphene-ω-carboxylic acid	66	57

[a] The yields are only approximate, the carbonation reaction having been used to demonstrate the presence of the alkenylmagnesium halide rather than as a preparation of the acid.

References

1. Behal and Sommelet, *Compt. rend.*, *138*, 89 (1904).
1a. Bartocha, B., F. E. Brinckman, H. D. Kaesz, and F. G. A. Stone, *Proc. Chem. Soc.*, *1958*, 116.
1b. Bartocha, B., and F. G. A. Stone, *Z. Naturforsch.*, *13B*, 348 (1948).
1c. Benary, E., *Ber.*, *64*, 2543 (1931).
2. Bidon, F., *Diplome Etudes Sup. Paris*, June 1955.
2a. Boekelheide, V., and G. C. Morisson, *J. Am. Chem. Soc.*, *80*, 3905 (1958).
3. Braude, E. A., and C. J. Timmons, *J. Chem. Soc.*, *1950*, 2000.
4. Braude, E. A., and C. J. Timmons, *J. Chem. Soc.*, *1950*, 2007.
5. Braude, E. A., and J. A. Coles, *J. Chem. Soc.*, *1950*, 2012.
6. Braude, E. A., and J. A. Coles, *J. Chem. Soc.*, *1950*, 2014.
7. Braude, E. A., and J. A. Coles, *J. Chem. Soc.*, *1951*, 2078.
8. Braude, E. A., and J. A. Coles, *J. Chem. Soc.*, *1952*, 1425.
9. Braude, E. A., and E. A. Evans, *J. Chem. Soc.*, *1955*, 3331.
9a. Braude, E. A., and E. A. Evans, *J. Chem. Soc.*, *1956*, 3333.
10. Busch, M., *Ber.*, *37*, 2691 (1904).
11. Carroll, M. F., *J. Chem. Soc.*, *1940*, 704.
12. Cerny, M., and R. Lukeš, *16th Intern. Congr. Pure Appl. Chem.*, *Congress Handbook*, Paris, July, 1957, p. 127.

12a. Lukeš, R., and M. Cerny, *Collection Czechoslov. Chem. Communs.*, *23*, 946 (1958).
12b. Curtin, D. Y., and J. W. Crump, *J. Am. Chem. Soc.*, *80*, 1922 (1958).
13. Colonge, J., and A. Perrot, *Compt. rend.*, *239*, 541 (1954).
14. Crisan, C., and H. Normant, *Bull. soc. chim. France*, *1957*, 1451.
14a. Cuvigny, Th., and H. Normant, *Compt. rend.*, *247*, 1744 (1958).
15. Delacre, M., *Bull. soc. chim. France*, *35*, 345 (1906).
16. Dreiding, A. S., and R. J. Pratt, *J. Am. Chem. Soc.*, *76*, 1902 (1954).
17. Eschenmoser, A., A. J. Schreiber, and S. A. Julia, *Helv. Chim. Acta*, *36*, 482 (1953).
18. Ficini, J., *Bull. soc. chim. France*, *1956*, 119.
19. Ficini, J., and H. Normant, *Bull. soc. chim. France*, *1957*, 1454.
19a. Ficini, J., and H. Normant, *Compt. rend.*, *247*, 1627 (1958).
20. Gilman, H., and F. Schulze, *J. Am. Chem. Soc.*, *47*, 2022 (1925).
21. Gilman, H., E. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.*, *51*, 1576 (1929).
22. Gilman, H., E. A. Zoellner, W. Selby, and C. Boatner, *Rec. trav. chim.*, *54*, 584 (1935).
23. Gilman, H., W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, *62*, 2327 (1940).
24. Gilman, H., and A. H. Haubein, *J. Am. Chem. Soc.*, *67*, 1420 (1945).
25. Gilman, H., and B. J. Gaj, *J. Org. Chem.*, *22*, 1166 (1957).
25a. Guillemonat, A., and Pelisser, *Bull. soc. chim. France*, *1958*, 431.
26. Iotsitch, *Bull. soc. chim. France*, *1905*, No. 3, 329.
27. Job and Reich, *Bull. soc. chim. France*, *1923*, 1414.
28. Jones, E. R. H., and B. C. L. Weedon, *J. Chem. Soc.*, *1946*, 937.
29. Jones, E. R. H., L. Skattebol, and M. C. Whiting, *J. Chem. Soc.*, *1956*, 4765.
30. Julia, M., *Ann. chimie (Paris)*, *5*, No. 12, 595 (1950).
31. Julia, M., and J. M. Surzur, *Bull. soc. chim. France*, *1956*, 1629.
31a. Julia, M., and J. Bullot, *Compt. rend.*, *246*, 3648 (1958).
31b. Jutz, C., *Chem. Ber.*, *91*, 1867 (1958).
32. Kharasch, M. S., and O. Reinmuth, *Grignard Reactions of Non-metallic Substances*, Prentice-Hall, New York, 1954, p. 6.
33. Ref. 32, p. 1052.
34. Kirrmann, A., *Compt. rend.*, *181*, 671 (1925).
35. Kirrmann, A., *Compt. rend.*, *184*, 1178 (1927).
36. Kirrmann, A., and R. Muths, *Compt. rend.*, *239*, 1807 (1954).
37. Krestinsky, W., *Ber.*, *55B*, 2754 (1922).
38. Levy, V., and H. Normant, *Compt. rend.*, *244*, 202 (1957).
39. Levy, V., Ph.D. Thesis, No. 568, Paris, 1958.
40. Lewis, R. N., and J. R. Wright, *J. Am. Chem. Soc.*, *74*, 1253 (1952).
41. Maier, L., D. Seyferth, F. G. A. Stone, and E. G. Rochow, *J. Am. Chem. Soc.*, *79*, 5884 (1957).
42. Maitte, P., Unpublished results.
42a. Maitte, P., *Bull. soc. chim. France*, *1959*, 499.
43. Martin, G., *Compt. rend.*, *245*, 1933 (1957).
44. Martin, G., *Ann. chimie (Paris)*, *13*, No. 4, 541 (1959).

44a. Miginiac, L., *Compt. rend.*, *247*, 2156 (1958).
45. Morton, A. A., F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, and R. L. Letsinger, *J. Am. Chem. Soc.*, *72*, 3785 (1950).
46. Nazarov, I. N., I. V. Torgov, and G. P. Verkholetova, *Doklady Akad. Nauk SSSR*, *112*, 1067 (1957); through *Chem. Abstr.*, *51*, 14647 (1957).
46a. Nesmeyanov, A. N., A. E. Borisov, and N. V. Novikova, *Doklady Akad. Nauk SSSR*, *119*, 504, 712 (1958); through *Chem. Abstr.*, *52*, 17093*e*, 17161*g* (1958).
47. Normant, H., *Compt. rend.*, *226*, 733 (1948).
48. Normant, H., *Bull. soc. chim. France*, *1950*, 739.
49. Normant, H., Fr. Pat. 656,917; requested 23-10-1953; accepted 14-1-1957; *Compt. rend.*, *239*, 1510 (1954).
50. Normant, H., *Compt. rend.*, *239*, 1811 (1954).
51. Normant, H., *Compt. rend.*, *240*, 314 (1955).
52. Normant, H., *Compt. rend.*, *240*, 440 (1955).
53. Normant, H., *Compt. rend.*, *240*, 631 (1955).
54. Normant, H., *Compt. rend.*, *240*, 1111 (1955).
55. Normant, H., *Compt. rend.*, *240*, 1435 (1955).
56. Normant, H., and C. Crisan, *Compt. rend.*, *241*, 1946 (1955).
57. Normant, H., and P. Maitte, *Bull. soc. chim. France*, *1956*, 1439.
58. Normant, H., and J. Ficini, *Bull. soc. chim. France*, *1956*, 1441.
59. Normant, H., and P. Maitte, *Bull. soc. chim. France*, *1956*, 951.
60. Normant, H., and P. Maitte, *Bull. soc. chim. France*, *1956*, 1439.
61. Normant, H., *Bull. soc. chim. France*, *1957*, 728.
62. Normant, H., and C. Crisan, *Compt. rend.*, *244*, 85 (1957).
63. Normant, H., and G. Martin, *Bull. soc. chim. France*, *1957*, 429.
64. Normant, H., *Bull. soc. chim. France*, *1957*, 1444.
65. Normant, H., and J. Ficini, Unpublished results.
66. Normant, H., Unpublished results.
66a. Normant, H., and Th. Cuvigny, *Bull. soc. chim. France*, *1957*, 1447.
66b. Normant, H., and J. Braun, *Compt. rend.*, *248*, 828 (1959).
67. Panouse, J. J., and C. Sannie, *Bull. soc. chim. France*, *1956*, 1279.
68. Paul, R., and H. Normant, *Bull. soc. chim. France*, *1943*, 484.
69. Petrov, A. D., *Bull. soc. chim. France*, *1956*, 1098.
69a. Petrov, A. D., and V. F. Mironov, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, *1957*, 1941.
70. Ramsden, H. E., Research Laboratory, Metal and Thermit Corp., Rahway, N. J., private communication, 1955.
70a. Ramsden, H. E., A. E. Balint, W. R. Witford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, *22*, 1202 (1957).
70b. Ramsden, H. E., J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint, and R. Cserr, *J. Org. Chem.*, *22*, 1602 (1957).
71. Raphael, R. A., *Acetylenic Compounds in Organic Synthesis*, Butterworths Scientific Publications, London, 1955, pp. 108–112.
71a. Reynolds, G. F., R. E. Dessy, and H. H. Jaffe, *J. Org. Chem.*, *23*, 1217 (1958).

72. Robinson, M., and R. Robinson, *J. Chem. Soc., 1923*, 532.
73. Rochow, E. G., *An Introduction to the Chemistry of the Silicones*, 2nd ed., John Wiley & Sons, Inc., New York, 1951, pp. 55, 100, 171, 178.
74. Rosenberg, S. D., J. J. Walburn, T. D. Stankovitch, A. E. Balint, and H. E. Ramsden, *J. Org. Chem., 22*, 1200 (1957).
75. Rosenberg, S. D., A. J. Gibbons, and H. E. Ramsden, *J. Am. Chem. Soc., 79*, 2137 (1957).
76. Rosenberg, S. D., and A. J. Gibbons, *J. Am. Chem. Soc., 79*, 2138 (1957).
76a. Saitow, A., E. G. Rochow, and D. Seyferth, *J. Org. Chem., 23*, 116 (1958).
77. Senkus, M., *J. Am. Chem. Soc., 67*, 1515 (1945).
78. Seyferth, D., and F. G. A. Stone, *J. Am. Chem. Soc., 79*, 515 (1957).
79. Seyferth, D., *J. Am. Chem. Soc., 79*, 2133 (1957).
80. Seyferth, D., *J. Org. Chem., 22*, 478 (1957).
81. Seyferth, D., *J. Org. Chem., 22*, 1252 (1957).
82. Seyferth, D., *J. Am. Chem. Soc., 79*, 2738 (1957).
83. Seyferth, D., *J. Am. Chem. Soc., 79*, 5881 (1957).
84. Tiffeneau, *Compt. rend., 135*, 1346 (1902).
84a. Vilkas, M., and N. A. Abraham, *Compt. rend., 246*, 1434 (1958).
85. Weyenberg, D. R., *Penn. State Org. Seminars Repts.*, May, 1956.
86. Wiberg and Coll, *Z. Naturforsch, B11*, 485, 487, 490 (1956).
87a. Wittig, G., and H. Witt, *Ber., 74*, 1474 (1941).
87b. Wittig, G., and J. Harborth, *Ber., 77*, 306 (1944).
88. Ziegler, K. *Ann., 434*, 75 (1923).

DIALKOXYDIHYDROFURANS AND DIACYLOXYDIHYDROFURANS AS SYNTHETIC INTERMEDIATES

By NIELS ELMING, *A/S Pharmacia, Copenhagen, Denmark*

CONTENTS

I. Introduction 67
II. 2,5-Dialkoxy-2,5-dihydrofurans 68
A. Preparation 68
B. *Cis-Trans* Isomerism 72
C. Reactions 72
D. Potential Applications of 2,5-Dialkoxy-2,5-dihydrofurans 103
III. 2,5-Diacyloxy-2,5-dihydrofurans 103
A. Preparation 103
B. *Cis-Trans* Isomerism 104
C. Reactions 105
IV. Experimental 107
A. 2,5-Dimethoxy-2,5-dihydrofuran 107
B. 2,5-Dimethoxytetrahydrofuran 110
C. Tropinone 110
D. 2,5-Diacetoxy-2,5-dihydrofuran 111
References 112

I. Introduction

In a paper published in 1947 Clauson-Kaas (5) discussed the reactions of the furan nucleus and in particular the 1,4-addition to furans of what may be termed oxidizing agents. It was shown that cyclic acetals of malealdehyde (e.g., 2,5-dimethoxy-2,5-dihydrofuran) are obtained by alkoxylation of furan, and another derivative of malealdehyde, 2,5-diacetoxy-2,5-dihydrofuran, was obtained in a similar way by 1,4-addition of two acetoxy groups to furan. The view was expressed that 2,5-dialkoxy-2,5-dihydrofurans and 2,5-diacetoxy-2,5-dihydrofuran represent new useful and important intermediates for synthetic organic chemistry. During the following 10 years these compounds have been used for many synthetic purposes. The present article deals with the chemistry and synthetic uses of these com-

pounds. Parts of the work in this field have been reviewed earlier (34,67,72,92,98,114,118). Patent literature will be mentioned in some cases, but in general the numerous patents covering this field will not be referred to.

II. 2,5-Dialkoxy-2,5-dihydrofurans

A. PREPARATION

The parent compound of the series, 2,5-dimethoxy-2,5-dihydrofuran (II), was prepared by Jones (68) and by Clauson-Kaas (5,26). When furan (I) was treated with a methanolic solution of bromine or chlorine in the presence of a weak base (e.g., potassium acetate, sodium carbonate, pyridine, etc.) it added two methoxy groups to form II.

(I) (II)

It was found (26) that a small amount (4%) of 2-methoxy-5-acetoxy-2,5-dihydrofuran was formed as a byproduct when potassium acetate was used. The alkoxylation of furan with higher alcohols gave the corresponding higher 2,5-dialkoxy-2,5-dihydrofurans (cf. Table I).

TABLE I
Unsubstituted 2,5-Dialkoxy-2,5-dihydrofurans

R	Yield, %	Ref.
Methyl	65	26
Ethyl	56, 79	5,51
n-Propyl	42	51
Isopropyl	70	26
n-Butyl	71, 65	26,51
Isoamyl	62	26

α-Substituted furans, such as 2-methylfuran, 2,5-dimethylfuran, furfuryl alcohol, furfuryl acetate, and furfural diacetate, can also be alkoxylated by the method described above (see Table II), but α-

substituted furans, such as furoic acid, ethyl furoate, ethyl furylacrylate and α-acetylfuran, with substituents which are known to decrease the reactivity of unsaturated systems, as a rule do not yield

TABLE II
α-Substituted 2,5-Dialkoxy-2,5-dihydrofurans

Starting material	Alcohol	Yield of corresponding 2,5-dialkoxy-2,5-dihydrofuran, %	Ref.
2-Methylfuran	Methanol	65	19
2-Methylfuran	Ethanol	66	51
2-Ethylfuran	Methanol	100	81
2-*n*-Propylfuran	Methanol	89	81
2-*n*-Butylfuran	Methanol	70	81; cf. 92a
2,5-Dimethylfuran	Methanol	60	81
2-Methyl-5-*n*-propylfuran	Methanol	52	81
Furfuryl alcohol[a]	Methanol	40	84
Furfuryl alcohol	Ethanol	49	51
Furfuryl acetate	Methanol	66	19
Furfural[a]	Methanol	60–70	84
Furfural diacetate	Methanol	81	13; cf. 88
Furfural diethyl acetal	Ethanol	70	51
Methyl furoate	Methanol	12	68
2-(Acetamidomethyl)furan	Methanol	80	14
sym-Difurfurylurea	Methanol	>68[b]	14
2-(Benzamidomethyl)furan	Methanol	27 + 31[c]	83a

[a] Meinel (84) believed his products to be 4,5-dimethoxy-4,5-dihydrofurfuryl alcohol and 4,5-dimethoxy-4,5-dihydrofurfural dimethyl acetal, but according to Clauson-Kaas (5) Meinel's compounds are the corresponding 2,5-derivatives.

[b] The 2,5-dimethoxy-2,5-dihydrofuran compound was not isolated, but used directly in a subsequent reaction.

[c] Both a solid isomer (27%) and a liquid isomer (31%) of 2,5-dimethoxy-2-benzamidomethyl-2,5-dihydrofuran were obtained.

the desired products (26). The only furan derivatives with an electronegative α-substituent which have been methoxylated by the above-mentioned procedure are furfural (84) and methyl furoate (68). But in the case of furfural, dimethoxydihydrofurfural dimethyl acetal was formed, so that probably acetalization or semiacetalization took place prior to methoxylation; in the case of methyl furoate, the

yield was only 12% of a product which boiled from 120–140° at 20 mm.

The alkoxylation reaction described above gives varying yields and, as a rule, special reaction conditions have to be worked out for each particular reaction. The reaction products are often contaminated by a small amount of halogen-containing impurities which may cause the formation of hydrogen halide and therefore greatly influence the stability of the acid-sensitive dimethoxydihydrofurans. These disadvantages were overcome by Clauson-Kaas' discovery of the electrolytic alkoxylation method (27). This reaction gives halogen-free, stable reaction products and can be carried out under standardized conditions. Pure dimethoxydihydrofurans (colorless liquids) prepared in this way have been stored for several years without deterioration or coloration.

The furan is mixed with an alcoholic solution of ammonium bromide and the mixture electrolyzed. Hydrogen and ammonia are formed at the cathode, and bromine is formed at the anode. The bromine reacts immediately with furan and alcohol to give 2,5-dialkoxy-2,5-dihydrofuran and hydrogen bromide. The hydrogen bromide and the ammonia from the cathode then regenerate ammonium bromide. The net equation for the synthesis of 2,5-dimethoxy-2,5-dihydrofuran (II) is

(II)

II was obtained in a 73% yield (27) (current efficiency 86%). A small amount of malealdehyde tetramethyl acetal was formed as a byproduct. When ethanol was used instead of methanol, 2,5-diethoxy-2,5-dihydrofuran was isolated (yield 63%; current efficiency 74%) together with a small amount of malealdehyde tetraethyl acetal (8).

Two convenient set-ups for the electrolytic alkoxylation of furans have been described, the one cell containing about 300 ml. (27), the other 10–50 ml. of electrolyte (83). The electrolytic method is also well adapted for larger scale operations. In a pilot plant operating with 8 kg. of furan, the yield of 2,5-dimethoxy-2,5-dihydrofuran was 84% (current efficiency 88%) (24).

As mentioned earlier, the nonelectrolytic alkoxylation method gives poor results with methyl furoate, and this is also the case when ammonium bromide is used as an electrolyte in the electrolytic methoxylation reaction, but, when sulfuric acid is used as an electrolyte, the desired electrolytic methoxylation takes place (20) (yield 68%). Murakami, Senoh, and Hata (85a,85b), describing hydrolytic experiments on furans, recently published the electrolytic

TABLE III
Electrolytic Methoxylation of Furans

Starting material	Yield of corresponding 2,5-dimethoxy-2,5-dihydrofuran, %	Ref.
Furan	73	27
2-Methylfuran	69	22
2-Hydroxymethylfuran	66	22
2-Methoxymethylfuran	83	7
2-Acetoxymethylfuran	87	22
2-Dimethoxymethylfuran	82	22
2-Carbomethoxyfuran	68	20
3-Isopropylfuran	72	38
2-Dimethoxymethyl-4-isopropylfuran	75	38
2-Carbomethoxy-4-isopropylfuran	61	38
2-(Acetamidomethyl)furan	96	31
2-(Carbomethoxyamidomethyl)furan	89	17
sym-Difurfurylurea	>85[a]	17
2-(α-Acetamidoethyl)furan	88	17
2-(α-Carbomethoxyamidoethyl)furan	88	17
2-(α-Ureidoethyl)furan	>62[a]	17
2-Acetylfuran	64	89
2-Carbomethoxy-5-isopropylfuran	87	87
2-Carbomethoxy-5-(*tert*-butyl)furan	97	87
2-(α-Hydroxyethyl)furan	73	87
2-(β,β-Dicarbomethoxyethyl)furan	74	40
2-(α-Acetoxy-β-acetamidoethyl)furan	>38[a]	87
2-(α-Acetamidoethyl)-3,4-bis(acetoxymethyl)furan	>76[a]	47
2-Acetoxymethyl-5-(acetamidomethyl)furan	>74[a]	48
2-(Benzamidomethyl)furan	27 + 47[b]	83a

[a] The 2,5-dimethoxy-2,5-dihydrofuran compound was not isolated, but used directly in a subsequent reaction.

[b] Both a solid isomer (27%) and a liquid isomer (47%) of 2,5-dimethoxy-2-benzamidomethyl-2,5-dihydrofuran were obtained.

ethoxylation of ethyl furoate. 2,5-Diethoxy-2-carbethoxy-2,5-dihydrofuran was formed in 55% yield.

It has been reported (32) that many electrolytes other than ammonium bromide and sulfuric acid (e.g., ammonium nitrate, sodium nitrate, sodium formate, and boron fluoride etherate) can be applied, but, in the case of the electrolytic methoxylation of furan itself, ammonium bromide gives the best yield.

Table III lists the electrolytic methoxylations carried out so far.

B. *CIS-TRANS* ISOMERISM

The 2,5-dimethoxy-2,5-dihydrofurans are usually mixtures of the *cis* and *trans* isomers (20,31). In three cases (the derivatives of 2-(acetamidomethyl)furan (31), of *sym*-difurfurylurea (17), and of 2-(benzamidomethyl)furan (83a)) one of the isomers has been isolated in a pure state by crystallization. In general, however, the 2,5-dimethoxy-2,5-dihydrofurans are used as intermediates for the preparation of 1,4-dicarbonyl compounds and are therefore not separated, since the isomers give the same dicarbonyl compounds on acid hydrolysis.

The parent 2,5-dimethoxy-2,5-dihydrofuran has been separated into the pure isomers (91) by fractional distillation through a 50 cm. packed column (21) under 90 mm of pressure. It was inferred from the infrared spectra that the purity of the isomers was higher than 95%. It was not determined which isomer was the *cis* and which was the *trans* isomer. The lower boiling isomer (yield 50% of distillate) has b.p.$_{90}$ 96.0°, n_D^{25} 1.4318 and the higher boiling isomer (yield 40% of distillate) b.p.$_{90}$ 98.5°, n_D^{25} 1.4331.

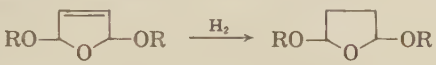
C. REACTIONS

From a synthetic point of view, the most important property of the 2,5-dialkoxy-2,5-dihydrofurans (and the corresponding 2,5-dialkoxytetrahydrofurans) is their ability to furnish 1,4-dicarbonyl compounds on acid hydrolysis. The 1,4-dicarbonyl compounds obtained have been transformed into useful products in a variety of ways. The reactions of the 1,4-dicarbonyl compounds may be divided into two types: (*1*) Intermolecular condensations with other molecules and and (*2*) intramolecular condensation between one of the carbonyl groups and the side chain present in the 2-substituted 2,5-dialkoxy-

2,5-dihydrofuran starting material. The 2,5-dialkoxy-2,5-dihydrofurans and the 2,5-dialkoxytetrahydrofurans, being cyclic acetals, are stable under alkaline and neutral conditions, and it is therefore possible to carry out many reactions with preservation of the ring system, before the desired acid hydrolysis is effected. In this way many 1,4-dicarbonyl compounds, hitherto difficult or impossible to prepare, have now been made easily accessible for further reactions.

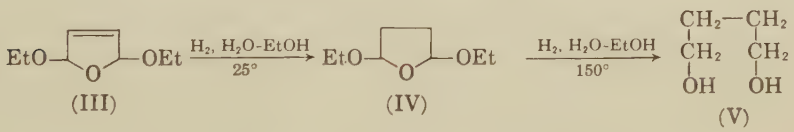
1. Hydrogenation: 2,5-Dialkoxytetrahydrofurans

On catalytic hydrogenation 2,5-dialkoxy-2,5-dihydrofurans give the corresponding 2,5-dialkoxytetrahydrofurans.



The hydrogenation of 2,5-dimethoxy-2,5-dihydrofuran was first reported by Jones (70), and the hydrogenation of 2,5-diethoxy-2,5-dihydrofuran was described by Fakstorp, Raleigh, and Schniepp (51). Later, many 2,5-dialkoxy-2,5-dihydrofurans have been catalytically hydrogenated (see Table IV). The reaction is usually carried out at room temperature in alcoholic solution with Raney nickel as the catalyst under high pressure, but other catalysts and lower pressures can also be applied.

Hydrogenolytic experiments with 2,5-diethoxy-2,5-dihydrofuran (III) have been described by Fakstorp, Raleigh, and Schniepp (51). III was hydrogenated over Raney nickel in an alcohol–water or a dioxane–water mixture to give 1,4-butanediol (V) in 50% yield. The reaction takes place in two distinct steps, involving the formation of 2,5-diethoxytetrahydrofuran (IV).



Some evidence was given to show that ethanol, tetrahydrofuran, and 2-ethoxytetrahydrofuran were formed on hydrogenolysis of III (Raney nickel at 150° in the absence of solvent).

Catalytic hydrogenation of the pure *cis-trans* isomers of 2,5-dimethoxy-2,5-dihydrofuran to the corresponding *cis-trans* isomers of 2,5-dimethoxytetrahydrofuran has been reported (91). The dif-

TABLE IV
Catalytic Hydrogenation of 2,5-Dialkoxy-2,5-dihydrofurans

Starting material	Yield of corresponding 2,5-dialkoxytetrahydrofuran, %	Ref.
2,5-Dimethoxy-2,5-dihydrofuran	85, 89	70,23
2,5-Diethoxy-2,5-dihydrofuran	97, 85	23,51
2,5-Di-*n*-propoxy-2,5-dihydrofuran	No yield reported	51
2,5-Di-*n*-butoxy-2,5-dihydrofuran	No yield reported	51
2,5-Diethoxy-2-methyl-2,5-dihydrofuran	No yield reported	51
2,5-Diethoxy-2-hydroxymethyl-2,5-dihydrofuran	No yield reported	51
2,5-Diethoxy-2-diethoxymethyl-2,5-dihydrofuran	No yield reported	51
2,5-Dimethoxy-2-methyl-2,5-dihydrofuran	81	46
2,5-Dimethoxy-2-ethyl-2,5-dihydrofuran	71	81
2,5-Dimethoxy-2-*n*-propyl-2,5-dihydrofuran	69	81
2,5-Dimethoxy-3-isopropyl-2,5-dihydrofuran	56	46
2,5-Dimethoxy-2-dimethoxymethyl-2,5-dihydrofuran	92	46
2,5-Dimethoxy-2-diacetoxymethyl-2,5-dihydrofuran[a]	81	88
2,5-Dimethoxy-2-carbomethoxy-2,5-dihydrofuran	91	20
2,5-Dimethoxy-2-hydroxymethyl-2,5-dihydrofuran	96	12
2,5-Dimethoxy-2-(α-hydroxyethyl)-2,5-dihydrofuran	87	87
2,5-Dimethoxy-2-methoxymethyl-2,5-dihydrofuran	93	7
2,5-Dimethoxy-2-acetoxymethyl-2,5-dihydrofuran	96	12
2,5-Dimethoxy-2-dimethoxymethyl-4-isopropyl-2,5-dihydrofuran	56	38
2,5-Dimethoxy-2-carbomethoxy-4-isopropyl-2,5-dihydrofuran	72	38
2,5-Dimethoxy-2-carbomethoxy-5-isopropyl-2,5-dihydrofuran	89	87
2,5-Dimethoxy-2-carbomethoxy-5-*tert*-butyl-2,5-dihydrofuran	94	87
2,5-Dimethoxy-2-acetamidomethyl-2,5-dihydrofuran	97	31
2,5-Dimethoxy-2-(α,α-dimethoxyethyl)-2,5-dihydrofuran	83	89

TABLE IV (*continued*)

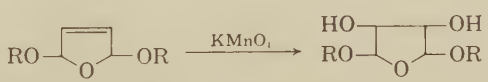
Starting material	Yield of corresponding 2,5-dialkoxytetra-hyhydrofuran, %	Ref.
2,5-Dimethoxy-2-(β,β-dicarbomethoxyethyl)-2,5-dihydrofuran	83	40
2,5-Dimethoxy-2-benzamidomethyl-2,5-dihydrofuran	94	83a

[a] Potts and Robinson (92a) subjected 2,5-dimethoxy-2-diacetoxymethyl-2,5-dihydrofuran to catalytic hydrogenation at room temperature and pressure in the presence of Raney nickel and obtained 5-methoxy-2-diacetoxymethyl-2,5-dihydrofuran in 80% yield. Further catalytic hydrogenation gave 2-(diacetoxymethyl)tetrahydrofuran.

ference in boiling point between the two isomers is 3° under atmospheric pressure. It is interesting to note that the lower boiling isomer of 2,5-dimethoxy-2,5-dihydrofuran gave the higher boiling isomer of 2,5-dimethoxytetrahydrofuran and vice versa. The data of the pure isomers of 2,5-dimethoxytetrahydrofuran prepared from the pure isomers of 2,5-dimethoxy-2,5-dihydrofuran were in agreement with those recorded on samples obtained by fractional distillation of technical 2,5-dimethoxytetrahydrofuran through a 50 cm. column under 100 mm. of pressure.

2. Hydroxylation: cis-3,4-Dihydroxy-2,5-dialkoxytetrahydrofurans

The hydroxylation of 2,5-dialkoxy-2,5-dihydrofurans was described by Clauson-Kaas (9,10; cf. also 74,102,123). When 2,5-dialkoxy-2,5-dihydrofurans are treated with potassium permanganate, *cis*-hydroxylation of the 3,4-double bond takes place, and *cis*-3,4-dihydroxy-2,5-dialkoxytetrahydrofurans are formed (see Table V).



The compounds have been used as intermediates for syntheses of tropinones by the Robinson-Schöpf method (see Section II-C-6).

From Table V it will be noted that the yields are rather low. It would be desirable to improve the yields of the hydroxylation reac-

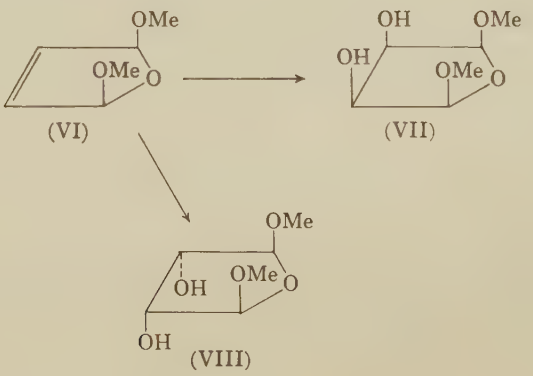
tion of dimethoxydihydrofurans, since a good general procedure for this reaction might open a simple route for the preparation of certain carbohydrates from furans.

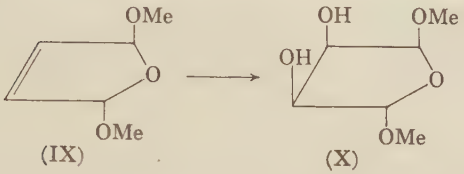
As indicated in Table V, the pure isomers of 2,5-dimethoxy-2,5-dihydrofuran have been *cis*-hydroxylated (91), and it is interesting

TABLE V
Cis-Hydroxylation of 2,5-Dialkoxy-2,5-dihydrofurans

Starting material	Yield of corresponding *cis*-3,4-dihydroxy-2,5-dimethoxy-tetrahydrofuran, %	Ref.
2,5-Dimethoxy-2,5-dihydrofuran, lower boiling isomer	44	91
2,5-Dimethoxy-2,5-dihydrofuran, higher boiling isomer	17	91
2,5-Diethoxy-2,5-dihydrofuran	29	10
2,5-Di-*n*-propoxy-2,5-dihydrofuran	18	10
2,5-Diisopropoxy-2,5-dihydrofuran	31	10
2,5-Dimethoxy-2-carbomethoxy-2,5-dihydrofuran	19	10
2,5-Dimethoxy-2-acetoxymethyl-2,5-dihydrofuran	10	10
2,5-Dimethoxy-2-dimethoxymethyl-2,5-dihydrofuran	3	10

to observe that there is a marked difference in the yield of the two *cis*-glycols. From the *cis* isomer (VI), two different *cis*-glycols (VII and VIII) can be imagined, whereas the *trans* isomer (IX) can only give one *cis*-glycol (X).

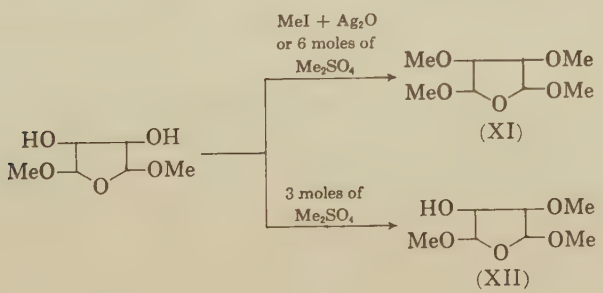




The experiments, however, showed that only one *cis*-glycol was obtained from each isomer. The *cis*-hydroxylation reaction, therefore, gave no direct information as to the *cis-trans* relationship between the isomers. Since one of the glycols must be a racemic form, that is, *d,l-cis*-3,4-dihydroxy-*trans*-2,5-dimethoxytetrahydrofuran (X), attempts to resolve the two glycols have been made (91). Chromatography of the *cis*-glycols on *d*-lactose according to the technique described by Prelog and Wieland (93) and on starch according to Krebs, Wagner, and Diewald (76) were unsuccessful. The *l*-methoxyacetates have been prepared, but turned out to be liquids. It was therefore not possible to separate any diastereomeric forms by fractional crystallization.

From the two *cis*-glycols, the corresponding diacetates have been prepared (91). One is crystalline (m.p. 97–98°), and the other is a liquid. The diacetate (m.p. 97–99°) described by Zeile and Heusner (123) apparently consists mainly of the crystalline diacetate just mentioned. Zeile and Heusner (123) made the interesting observation that the diacetate is so stable to acid hydrolysis that it is possible to recrystallize it from dilute hydrochloric acid.

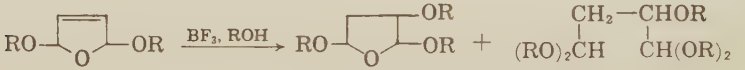
Kebrle and Karrer (74) methylated *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran with methyl iodide in the presence of silver oxide to 2,3,4,5-tetramethoxytetrahydrofuran (XI). Zeile and Heusner (123) prepared the same compound using 6 moles of dimethyl sulfate.



With 3 moles of dimethyl sulfate they obtained 2,3,5-trimethoxy-4-hydroxytetrahydrofuran (XII) together with starting material.

3. Addition of Alcohols to the 3,4-Double Bond: 2,3,5-Trialkoxytetrahydrofurans

Stoll, Lindenmann, and Jucker (111) described the preparation of 2,3,5-trialkoxytetrahydrofurans by interaction of equimolar amounts of 2,5-dialkoxy-2,5-dihydrofurans and hydrogen bromide in alcoholic solution. It was suggested that the reaction took place through an intermediate 2,5-dialkoxy-3-bromotetrahydrofuran in which the bromine was replaced by a metathetic reaction with the solvent. Clauson-Kaas, Nielsen, and Boss (30) prepared 2,3,5-trimethoxytetrahydrofuran and 2,3,5-triethoxytetrahydrofuran by interaction of the alcohol and the dialkoxydihydrofuran in the presence of an acid catalyst, preferably boron fluoride etherate (cf. 11). At the same time a certain amount of the tetraalkyl acetal of the alkoxysuccindialdehyde was formed. The reaction products were separated by fractional distillation.



55% (R = Et) 16% (R = Et)
33% (R = Me) 32% (R = Me)

The view has been put forward (30) that the experiments of Stoll, Lindenmann, and Jucker (111) are also acid-catalyzed alcoholic additions rather than two-step reactions proceeding through an intermediate bromo compound.

Stoll, Lindenmann, and Jucker (111) also described a method by which furan was used directly as a starting material, and they reported the transformation of 2,5-diethoxy-2,5-dihydrofuran into 2,3,5-trimethoxytetrahydrofuran, 2,3,5-triethoxytetrahydrofuran, 2,3,5-

TABLE VI
Preparation of 2,3,5-Trialkoxytetrahydrofurans

2,3,5-Trialkoxytetrahydrofuran	Yield, %	Ref.
2,3,5-Trimethoxytetrahydrofuran	59	111, cf. 30
2,3,5-Triethoxytetrahydrofuran	68	111, cf. 30
2,3,5-Tri-*n*-propoxytetrahydrofuran	58	111
2,3,5-Triisopropoxytetrahydrofuran	54	111

tri-*n*-propoxytetrahydrofuran, and 2,3,5-triisopropoxytetrahydrofuran (see Table VI). 2,3,5-Trialkoxytetrahydrofurans have been used as starting materials for the syntheses of 6-alkoxytropinones; see Section II-C-6.

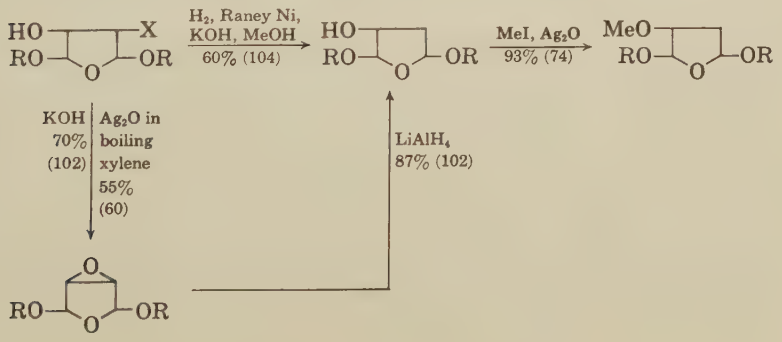
4. Addition of Hypohalogeneous Acids to the 3,4-Double Bond: 2,5-Dialkoxy-3-halogeno-4-hydroxytetrahydrofurans

Stoll, Becker, and Jucker (104) showed that hypohalogeneous acids, under suitable reaction conditions, add to the 3,4-double bond of 2,5-dialkoxy-2,5-dihydrofurans to furnish 2,5-dialkoxy-3-halogeno-4-hydroxytetrahydrofurans. Sheehan and Bloom (102), Ginsburg (60), and Kebrle and Karrer (74) have described similar reactions.

TABLE VII
Preparation of 2,5-Dialkoxy-3-halogeno-4-hydroxytetrahydrofurans

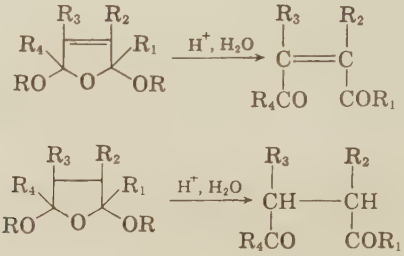
2,5-Dialkoxy-3-halogeno-4-hydroxy-tetrahydrofuran	Yield, %	Ref.
2,5-Dimethoxy-3-chloro-4-hydroxytetrahydrofuran	96, 75, 58	60,74,102
2,5-Diethoxy-3-chloro-4-hydroxytetrahydrofuran	70	104
2,5-Diethoxy-3-bromo-4-hydroxytetrahydrofuran	No yield reported	104
2,5-Diisopropoxy-3-chloro-4-hydroxytetrahydrofuran	No yield reported	104

2,5-Dialkoxy-3-halogeno-4-hydroxytetrahydrofurans have been transformed into other products of interest in the tropane alkaloid field (60,74,102,104); see Section II-C-6).



5. *Hydrolysis Followed by Intermolecular or Intramolecular Condensation*

The ring system of the 2,5-dialkoxy-2,5-dihydrofurans and 2,5-dialkoxytetrahydrofurans is stable under alkaline and neutral conditions. On acid hydrolysis the ring is opened and 1,4-dicarbonyl compounds are formed.



In most cases the dicarbonyl compounds have been identified as bisphenylhydrazones, bisdinitrophenylhydrazones, bismethylphenylhydrazones, or bisdiphenylhydrazones.

If the dicarbonyl compounds are sufficiently stable, they may be obtained in a pure state, and this has been done in a few cases. Jones (69,71) reported the isolation of malealdehyde (by hydrolysis of 2,5-dimethoxy-2,5-dihydrofuran) as an oil, but gave no analysis or description. In an attempt to synthesize tropolone from malealdehyde, Hufford, Tarbell, and Koszalka (66) isolated malealdehyde from the acid hydrolysis mixture of 2,5-dimethoxy-2,5-dihydrofuran by partition chromatography of the mixture on silicic acid. A yellow oil was obtained, consisting of malealdehyde and unchanged 2,5-dimethoxy-2,5-dihydrofuran. From this oil could be isolated, in some runs, up to 27% of a yellow crystalline solid, m.p. 42–44° (apparently identical with the crystalline compound, m.p. 40–43° reported by Wohl and Mylo, 119), which was first regarded as crystalline malealdehyde, but further work brought the view that it was fumaric dialdehyde, formed from the oily malealdehyde in some runs by isomerization.

Fakstorp, Raleigh, and Schniepp (51) isolated succinic aldehyde from 2,5-diethoxytetrahydrofuran in 30% yield.

Levisalles (81) hydrolyzed 2,5-dimethoxy-2,5-dimethyl-2,5-dihydrofuran with 1% acetic acid and isolated *cis*-3-hexene-2,5-dione in 69% yield. When the hydrolysis was carried out with concentrated

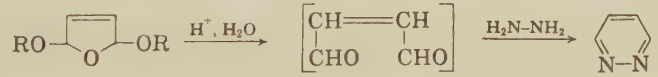
hydrochloric acid *trans*-3-hexene-2,5-dione was obtained. It was demonstrated that, when *cis*-3-hexene-2,5-dione was dissolved in methanol and a drop of concentrated hydrobromic acid added, it rearranged into *trans*-3-hexene-2,5-dione.

Marei and Raphael (83a), in a recent work concerned with the synthesis of amino acids from furfurylamine, treated 2,5-dimethoxy-2-benzamidomethyl-2,5-dihydrofuran with chromium trioxide in dilute sulfuric acid and isolated 5-benzamido-4-oxopent-2-enoic acid. (Many attempts at a preliminary hydrolysis with acid alone, in order to isolate the intermediate keto-aldehyde, were unsuccessful.) A similar treatment of 2,5-dimethoxy-2-benzamidomethyltetrahydrofuran gave δ-benzamidolevulic acid.

As a rule, the 1,4-dicarbonyl compounds are not isolated, but the aqueous solutions containing the 1,4-dicarbonyl compounds are used directly for further syntheses consisting of intermolecular or intramolecular condensations. These reactions constitute the most important uses of 2,5-dialkoxy-2,5-dihydrofurans and 2,5-dialkoxytetrahydrofurans as synthetic intermediates, and these substances can be regarded as stable "depot compounds" for the labile 1,4-dicarbonyl compounds

6. Intermolecular Condensations

(*a*) *Pyridazines.* The reaction between unsaturated *cis*-1,4-dicarbonyl compounds, obtained by acid hydrolysis of 2,5-dialkoxy-2,5-dihydrofurans, and hydrazine represents a convenient synthesis of pyridazines (cf. Table VIII).



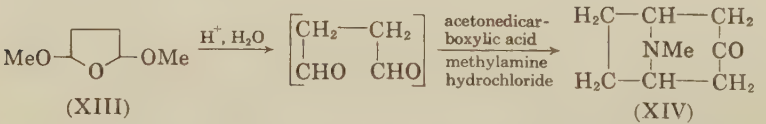
(*b*) *Tropinones.* The synthesis of tropinones by the method of Robinson (96), as modified by Schöpf and Lehmann (100), involves the condensation of 1,4-dicarbonyl compounds with acetonedicarboxylic acid and methylamine hydrochloride to form the tropane skeleton. (cf. also 73a). The major difficulty usually encountered in the synthesis of the more complex tropane alkaloids is the preparation of the appropriate 1,4-dicarbonyl compounds. The 2,5-dialkoxytetrahydrofurans represent excellent starting materials for tropinone syntheses. On acid hydrolysis they give the corresponding 1,4-dicarbonyl

TABLE VIII
Preparation of Pyridazines from 2,5-Dialkoxy-2,5-dihydrofurans

Starting material	Reaction product	Yield, %	Ref.
2,5-Dimethoxy-2,5-dihydrofuran	Pyridazine	80	80
2,5-Dimethoxy-2-methyl-2,5-dihydrofuran	3-Methylpyridazine	55, 55	19,80
2,5-Dimethoxy-2-ethyl-2,5-dihydrofuran	3-Ethylpyridazine	46	81
2,5-Dimethoxy-2-*n*-propyl-2,5-dihydrofuran	3-*n*-Propylpyridazine	44	81
2,5-Dimethoxy-3-isopropyl-2,5-dihydrofuran	4-Isopropylpyridazine	19	38
2,5-Dimethoxy-2-*n*-butyl-2,5-dihydrofuran	3-*n*-Butylpyridazine	49	81
2,5-Dimethoxy-2,5-dimethyl-2,5-dihydrofuran	3,6-Dimethylpyridazine	57, 32	80,82
2,5-Dimethoxy-2-methyl-5-*n*-propyl-2,5-dihydrofuran	3-Methyl-6-*n*-propylpyridazine	27	81
2,5-Dimethoxy-2-acetoxymethyl-2,5-dihydrofuran	3-Hydroxymethylpyridazine	49	19

compounds, which, without isolation, can be used directly in the tropane synthesis. In the following, examples of tropane syntheses starting from 2,5-dialkoxytetrahydrofurans will be given. A discussion of the many important works on the stereochemical relationships of the tropane derivatives lies outside the scope of this article. Recent excellent reviews of this field are available (53–55a,64,106; cf. also 63).

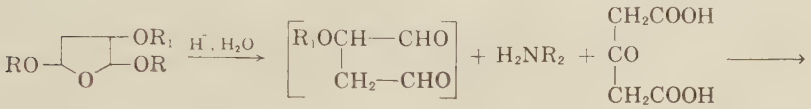
(*1*) *Tropinone.* Tropinone itself (XIV) has been prepared from 2,5-dimethoxytetrahydrofuran (XIII) (59) and from 2,5-diethoxytetrahydrofuran (52,85).

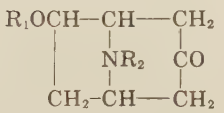


(XIII) (XIV)

It is not imperative to work under so-called "biogenetic conditions" (low concentrations, room temperature, long reaction time) generally considered necessary in the Robinson-Schöpf syntheses. XIV has been prepared in a yield of 81% by using high concentrations of the reactants at 60°, the reaction time being 1½ hr. (50,50a); see Section IV-C.

(*2*) *6-Alkoxytropinones.* 2,3,5-Trialkoxytetrahydrofurans (see Section II-C-3) have been used as starting materials for the syntheses of a variety of 6-alkoxytropinones (108,109; cf. also 73,105,106).

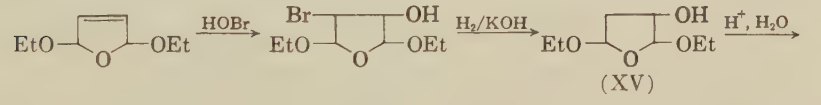




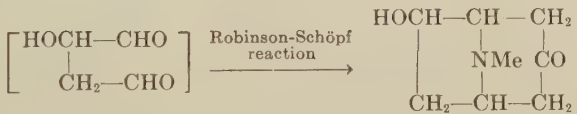
R = Me, Et
R_1 = Me, Et, *i*-Pr
R_2 = Me, Et, Pr, Bu, CH_2CH_2OH, $CHCH_2CH_3$ | CH_2OH, $C_6H_5CH_2$

The 6-alkoxytropinones were reduced to 6-alkoxytropines, which were esterified by various acids; many other compounds containing the tropane skeleton were also prepared (107–110; cf. also 73,105,106) Pharmacological work in this field has been published (97; cf. also 105,106).

(*3*) *6-Hydroxytropinone; total synthesis of scopine, scopolamine, and hyoscine.* Stoll, Becker, and Jucker (104; cf. also 112) synthesized 6-hydroxytropinone (XVII) by the following sequence of reactions (see Section II-C-4), involving 2,5-diethoxy-3-hydroxytetrahydrofuran (XV) as the source of the requisite hydroxysuccinaldehyde (XVI).

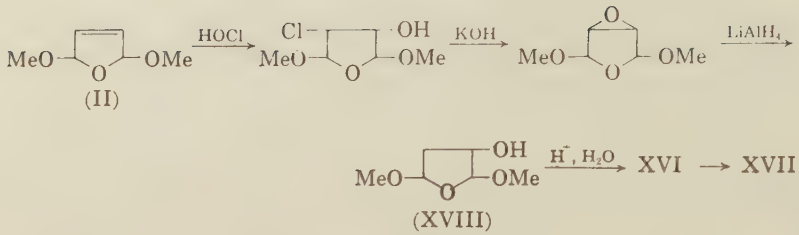


(XV)



(XVI) (XVII)

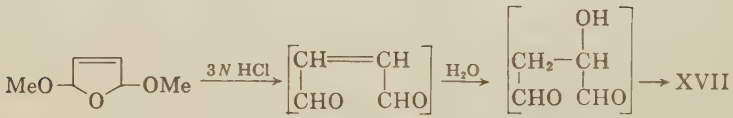
Sheehan and Bloom (102) also used XVI as the dicarbonyl derivative (see Section II-C-4), which they obtained from 2,5-dimethoxy-3-hydroxytetrahydrofuran (XVIII).



(II) (XVIII)

(over-all yield 7%)

A much simpler synthesis of XVII from 2,5-dimethoxy-2,5-dihydrofuran (II) has been described by Nedenskov and Clauson-Kaas (86), who showed that if an acid solution (3*N* HCl) of II is left standing for 18 hr. at room temperature, neutralized, and added to a buffered solution of methylamine and acetonedicarboxylic acid, XVII is obtained in a 45% yield. Apparently malealdehyde (XIX), which is formed very rapidly by hydrolysis of II, adds one mole of water, whereby hydroxysuccinaldehyde (XVI) is formed, which then participates in the Robinson-Schöpf reaction.



(II) (XIX) (XVI)

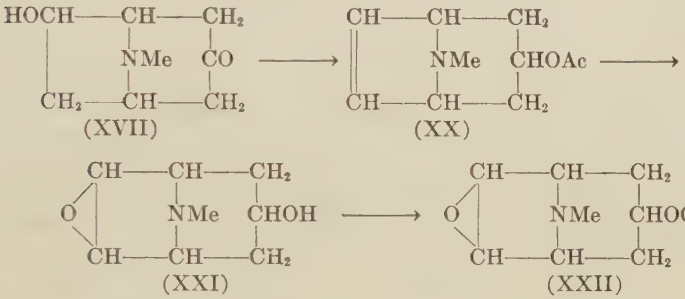
(over-all yield 45%)

Van Tamelen, Barth, and Lornitzo (113), in connection with their work on the conversion of 6-hydroxytropinone methiodide to tropone, further simplified the procedure by regenerating the free base XVII from the picrate (in which form the product is isolated from the reaction mixture) through the use of Dowex 2 in the basic phase.

Kebrle and Karrer (74) methylated XVIII to 2,3,5-trimethoxytetrahydrofuran (see Section II-C-4). This reaction gives another route to 6-alkoxytropinones. However, the method described in Section II-C-3 for the preparation of 2,3,5-trialkoxytetrahydrofurans is in general simpler and gives higher yields.

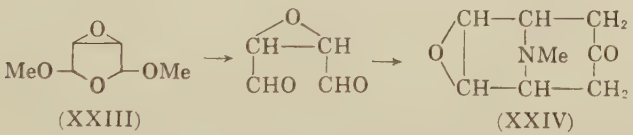
XVII has been applied by Fodor, Tóth, Koczor, Dobó, and Vincze (56; cf. 57) in the first total synthesis of scopine (XXI) and scopolamine (XXII). XVII was converted into tropenyl acetate (XX) by a six-step reaction. The trifluoroacetate of XX in acetonitrile was then

oxidized with pertrifluoroacetic acid in methylene chloride and the resulting scopyl acetate subjected to Kunz hydrolysis (acetone solution, one equivalent of sodium hydroxide, 20°, 2 days), whereby scopine (XXI) was obtained. Heating scopine hydrochloride for 4 days at 60° with a large excess of acetyltropeyl chloride in suspension in nitrobenzene furnished acetylscopolamine, which was deacylated to scopolamine (XXII), isolated as its hydrochloride.



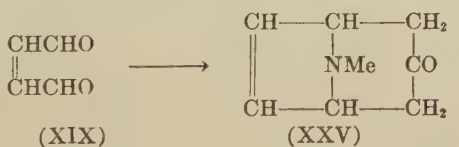
Since scopolamine (XXII) has already been resolved, the synthesis constitutes a total synthesis of hyoscine also.

In connection with this first total synthesis of scopolamine it is interesting to note that earlier attempts to synthesize scopolamine have failed. Sheehan and Bloom (102) were unsuccessful in attempts to use 2,5 - dimethoxy-3,4-*cis*-oxidotetrahydrofuran (XXIII) for a synthesis of scopinone (XXIV) (cf. 101).



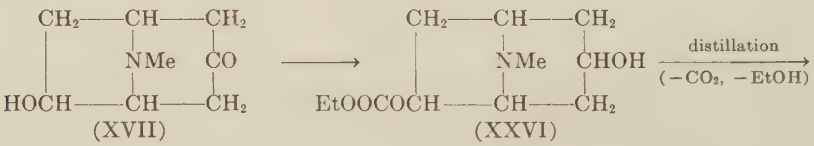
(unsuccessful)

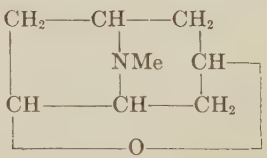
Preobrazhenskiĭ, Rubtsov, Dankova, and Pavlov (94) reported the following approach consisting of a Robinson-Schöpf reaction using malealdehyde (XIX) to give tropenone (XXV).



Unfortunately, however, the preparation of XXV from XIX has never been successful in the hands of other authors (25,74,105), and it has been suggested by Schöpf (cf. 53) that the product seems to have consisted of impure tropinone.

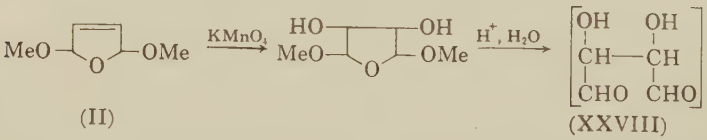
XVII has also been used for a synthesis of desoxyscopoline (XXVII) (121). Treatment of XVII with ethyl chloroformate gave 6-carbethoxyhydroxytropinone, which was reduced to 6-carbethoxyhydroxytropine (XXVI). On distillation at atmospheric pressure, carbon dioxide and ethanol were split off, and desoxyscopoline (XXVII) was obtained in a 30% yield.



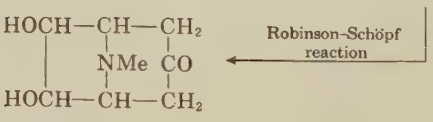


(XXVII)

(*4*) *cis-6,7-Dihydroxytropinone* (*teloidinone*) *and derivatives: synthesis of scopoline.* Teloidinone (XXIX), which has been synthesized by Schöpf and Arnold (99) from *meso*-tartaric dialdehyde (XXVIII), was prepared by Sheehan and Bloom (102) from 2,5-dimethoxy-2,5-dihydrofuran (II) (cf. Section II-C-2).



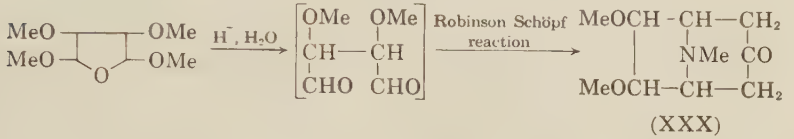
(II) (XXVIII)



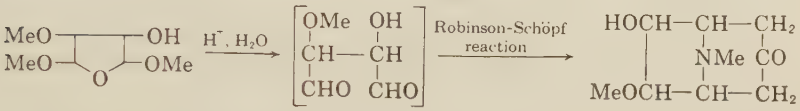
(XXIX) (*cis*)

The dimethoxy and monomethoxy derivatives of XXIX, that is, *is*-6,7-dimethoxytropinone (XXX) and *cis*-6-hydroxy-7-methoxy-

tropinone (XXXI) have been synthesized from 2,3,4,5-tetramethoxytetrahydrofuran (74,123) and 2,3,5-trimethoxy-4-hydroxytetrahydrofuran (123; cf. 65), respectively (cf. Section II-C-2).

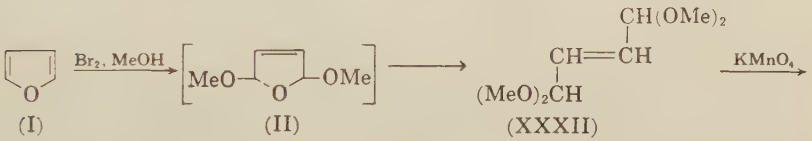


(XXX)

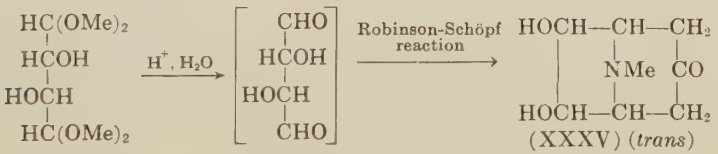


(XXXI)

In teloidinone (XXIX) the two hydroxy groups are in the *cis* position. The corresponding *d,l-trans*-6,7-dihydroxytropinone (XXXV) has been obtained by Zeile and Heusner (120) by an interesting synthesis (cf. also 63a,103a).



(I) (II) (XXXII)



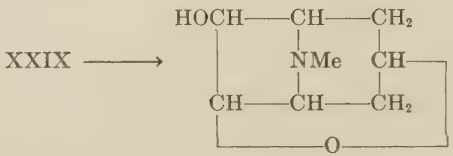
(XXXIII) (XXXIV) (XXXV) (*trans*)

When furan (I) was treated with methanol and bromine at about $-35°$ and the reaction mixture then neutralized with ammonia (temperature below $-10°$) to a pH of about 7 (cf. 116), fumaric dialdehyde tetramethyl acetal (XXXII) was obtained. Hydroxylation of XXXII with potassium permanganate gave *d,l*-tartaric dialdehyde tetramethyl acetal (XXXIII). XXXIII was hydrolyzed to *d,l*-tartaric dialdehyde (XXXIV) (not isolated), which finally was used in the Robinson-Schöpf synthesis to give XXXV.

The structures XXXIII and XXXIV were proved in the following way: Acid hydrolysis of XXXIII gave a dihydroxysuccindialdehyde

(XXXIV), the bisphenylhydrazone (m.p. 169°) of which was different from the known bisphenylhydrazone (m.p. 197.5°) of *meso*-tartaric dialdehyde (XXVIII). Oxidation of XXXIV with bromine water gave *d,l*-tartaric acid. An analogous oxidation of XXVIII gave *meso*-tartaric acid. These reactions prove that XXXIII is *d,l*-tartaric dialdehyde tetramethyl acetal and that XXXIV is *d,l*-tartaric dialdehyde; therefore, it can be concluded that XXXII is fumaric dialdehyde tetramethyl acetal. From the *threo* configuration of XXXIV it follows that the hydroxy groups in the new 6,7-dihydroxytropinone (XXXV) are in the *trans* position.

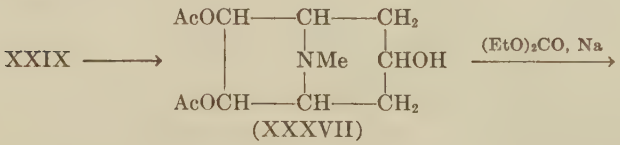
Further synthetic work in this field has resulted in a new synthesis of scopoline (XXXVI) from teloidinone (XXIX) (121).



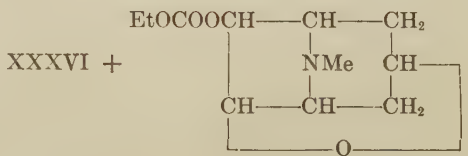
(XXXVI)
(over-all yield 35%)

Heating of XXIX with diethyl carbonate and sodium gave the cyclic carbonate of XXIX. Reduction furnished teloidine carbonate, which gave XXXVI on pyrolysis.

Another route to scopoline (XXXVI) from XXIX proceeds via teloidinone diacetate, which was reduced stereospecifically, and the resulting teleoidine 6,7-diacetate (XXXVII) gave, on interaction with diethyl carbonate and sodium, a mixture of XXXVI and carbethoxyscopoline (XXXVIII).



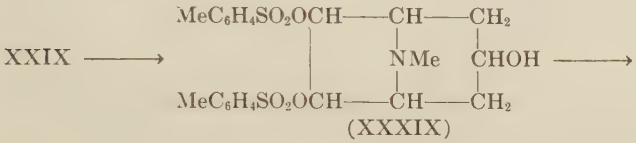
(XXXVII)

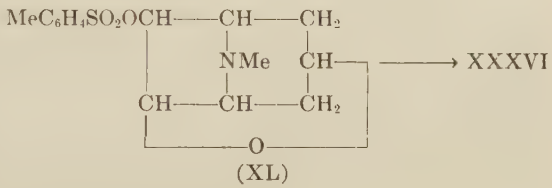


(XXXVIII)

After hydrolysis of XXXVIII to XXXVI, the over-all yield from XXIX was about 55%.

In a further modification of the scopoline synthesis (122; cf. 65), XXIX was converted into its di-*p*-tosyl ester, which was catalytically hydrogenated to teloidine di-*p*-tosyl ester (XXXIX). Interaction of XXXIX with 1 mole of sodium methoxide gave scopoline *p*-tosyl ester (XL), which was hydrolyzed to scopoline (XXXVI).

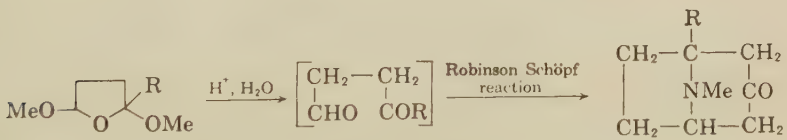




(over-all yield 50–60%)

Various new esters and substituted phenylurethanes of scopoline were also prepared and pharmacologically investigated (122).

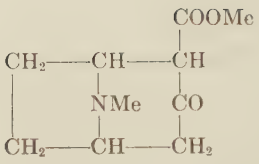
(*5*) *Some other substituted tropinones.* Kebrle and Karrer (74) prepared some 1-substituted tropinones from 2-substituted 2,5-dimethoxytetrahydrofurans.



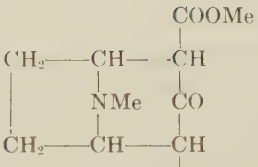
R = CH_2OH, CH_2OMe

When R = COOMe in the starting material, 1-carboxytropinone was obtained. Esterification yielded 1-carbomethoxytropinone.

In a synthetic study on 2-carbomethoxytropinone (XLI), a key intermediate for the synthesis of cocaine, Findlay (52) reported the use of 2,5-diethoxytetrahydrofuran as a source of succinaldehyde for the preparation of XLI and 2,4-dicarbomethoxytropinone (XLII).



(XLI)

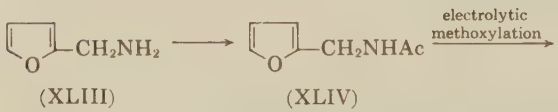


(XLII)

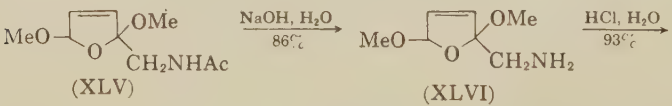
7. Intramolecular Condensations

Furans with suitable substituents in the 2-position may be transformed into other systems with aromatic character by alkoxylation to cyclic acetals of 1,4-dicarbonyl compounds, followed by intramolecular condensation in acid solution. Application of this principle has led to the transformation of furans into such substances as 3-pyridinols, 2,3-pyridinediols, cyclic hydroxamic acids, and benzenoid compounds.

(*a*) *3-Pyridinols.* From Table III it is seen that 2-(α-aminoalkyl)-furans can be methoxylated after acylation of the amino group (electrolytic methoxylation of furfurylamine (XLIII) with an unprotected amino group gives only a low yield of the corresponding dimethoxydihydrofuran (17)), and this reaction has opened new routes for the preparation of 3-pyridinols from furans. The following sequence of reactions showing the synthesis of 3-pyridinol (XLVIII) is illustrative (17).



(XLIII) (XLIV)



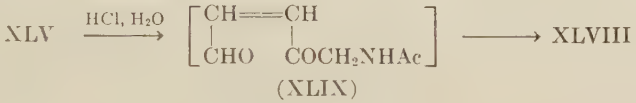
(XLV) (XLVI)

(XLVII) (XLVIII)

(over-all yield 73%)

Furfurylamine (XLIII) was acetylated and 2-(α-acetamidomethyl) furan (XLIV) then electrolytically methoxylated to XLV. Alkaline hydrolysis of XLV gave XLVI, which by boiling with 1*N* hydrochloric acid was transformed into 3-pyridinol (XLVIII). It is evident that XLVI is first hydrolyzed to the *cis*oid dicarbonylamine (XLVII), which then, by intramolecular condensation and aromatization, gives XLVIII.

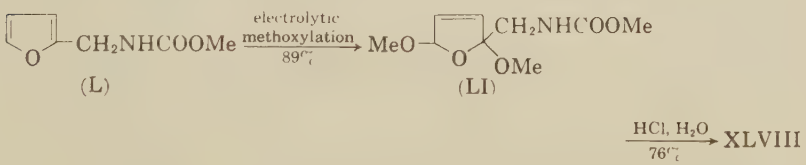
XLVIII has also been obtained by boiling XLV with hydrochloric acid, but the yield was only 50% and the reaction mixture turned dark red.



(XLIX)

(over-all yield 46% from XLIII)

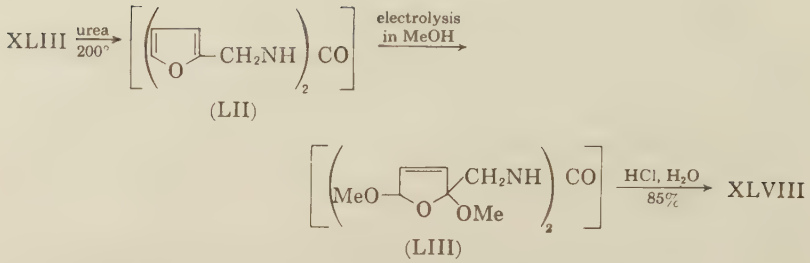
The explanation has been put forward (17) that the intramolecular condensation of the intermediate dicarbonylamide (XLIX) proceeds more slowly than the condensation of the dicarbonylamine (XLVII), since the former must involve initial hydrolysis of the amide function. Part of the dicarbonylamide (XLIX) therefore reacts differently due to the prolonged reaction time. Consistent with this assumption is the fact that an easily hydrolyzed acyl derivative of XLIV, the carbamate (LI), which was prepared by electrolytic methoxylation of the corresponding furan (L) gave, by boiling with hydrochloric acid, a higher yield of XLVIII (76%).



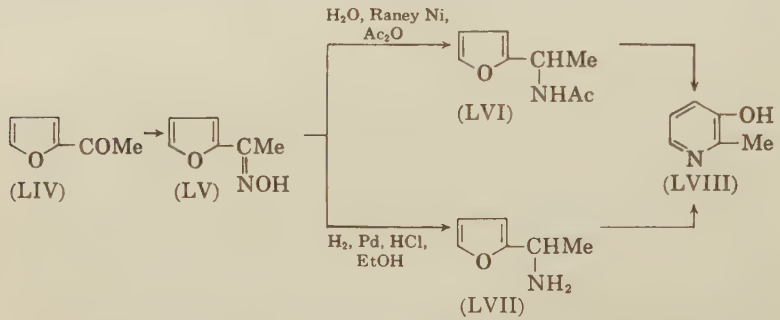
(L) (LI)

(over-all yield 55% from XLIII)

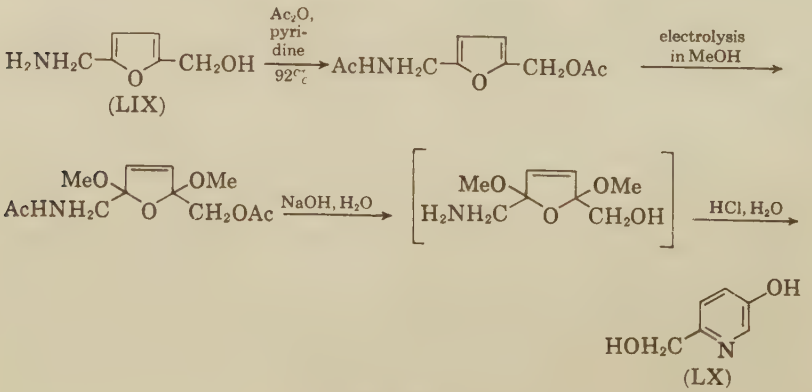
The above yields of XLVIII based upon furfurylamine (XLIII) were 73, 46, and 55%, respectively. However, by proceeding through *sym*-difurfurylurea (LII) and the corresponding dimethoxydihydrofuran (LIII), an 85% yield of XLVIII has been obtained by the following reaction sequence, in which the pure intermediates need not be isolated (17).



By similar reactions 2-methyl-3-pyridinol (LVIII) has been prepared from 2-acetylfuran (LIV), which, via 2-acetylfuran oxime (LV), was first converted into 2-(α-acetamidoethyl)furan (LVI) or 2-(α-aminoethyl)furan (LVII) (17).

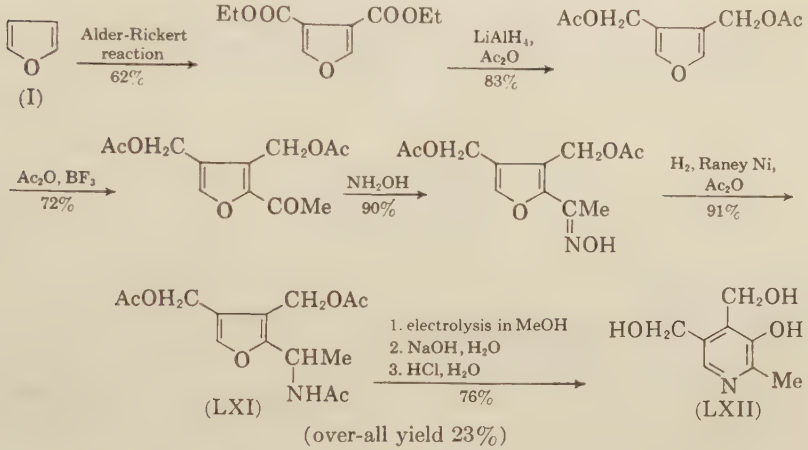


Another example is the synthesis of 6-hydroxymethyl-3-pyridinol (LX) from 2-(hydroxymethyl)-5-(aminomethyl)furan (LIX) by the following route (48).



(over-all yield 68%)

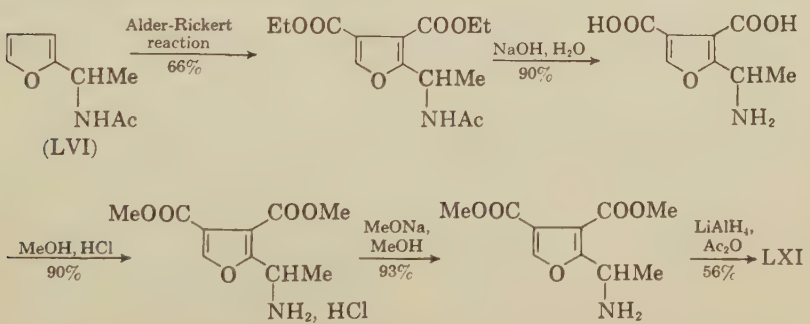
An important application of the 3-pyridinol synthesis has led to a new synthesis of pyridoxine (LXII) (47) from furan (I).



(over-all yield 23%)

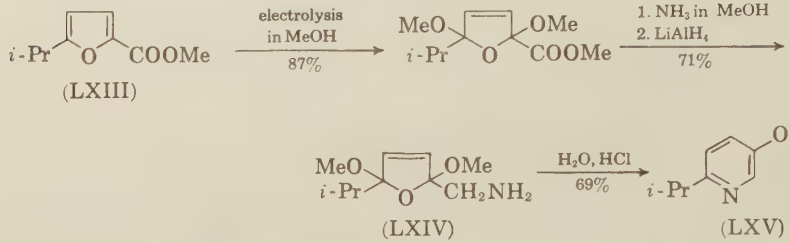
Attempts to transform 2-acetyl-3,4-bis(acetoxymethyl)furan into LXII by reaction with ammonia or ammonium salts failed (15). Similar observations have been published by Kornfeld (75) and by Williams, Kaufmann, and Mosher (117). Webb (115) claims that LXII is formed by this reaction, but no LXII was isolated.

In a modification of the new pyridoxine synthesis (16), 2-(α-acetamidoethyl)furan (LVI) was used as a starting material for the preparation of the intermediate LXI.



A useful variation of the 3-pyridinol synthesis has been reported by Clauson-Kaas and Nedenskov (28), who showed that 2-carbomethoxyfurans can be applied as starting materials. The principle is

illustrated by the preparation of 6-isopropyl-3-pyridinol (LXV) from 2-carbomethoxy-5-isopropylfuran (LXIII).



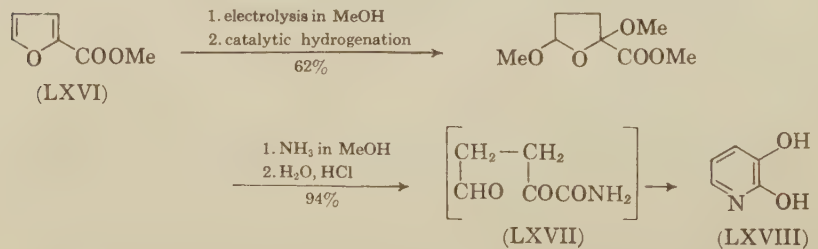
(LXIII) (LXIV) (LXV)

The carbomethoxy group in the methoxylation product was converted into an amide group, and reduction by lithium aluminum hydride furnished the desired primary amine (LXIV).

The 3-pyridinol syntheses described above all involve an electrolytic methoxylation step—with or without subsequent isolation of the methoxylation product—but it has been found, as expected, that the previously described nonelectrolytic alkoxylation method (see Section II-A) is also effective for the transformation of furans into 3-pyridinols (14).

An interesting modification of the method for the preparation of 3-pyridinol (XLVIII) consists simply in interaction of furfurylamine with chlorine or bromine in methanol–water, whereby XLVIII is formed directly (14).

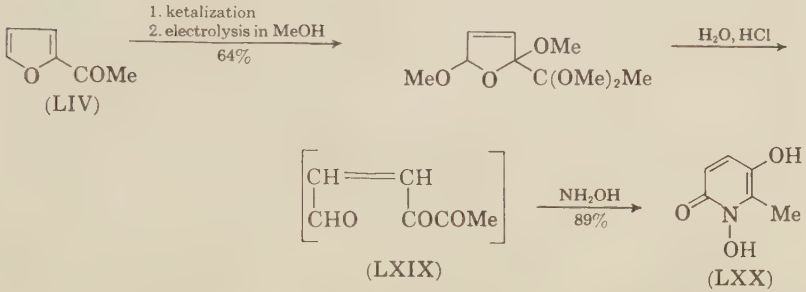
(*b*) *2,3-Pyridinediol.* 2,3-Pyridinediol (LXVIII) has been prepared from 2-carbomethoxyfuran (LXVI) by a new method (28), which involves the intramolecular condensation and aromatization of a reactive intermediate such as LXVII or its equivalent.



(LXVI) (LXVII) (LXVIII)

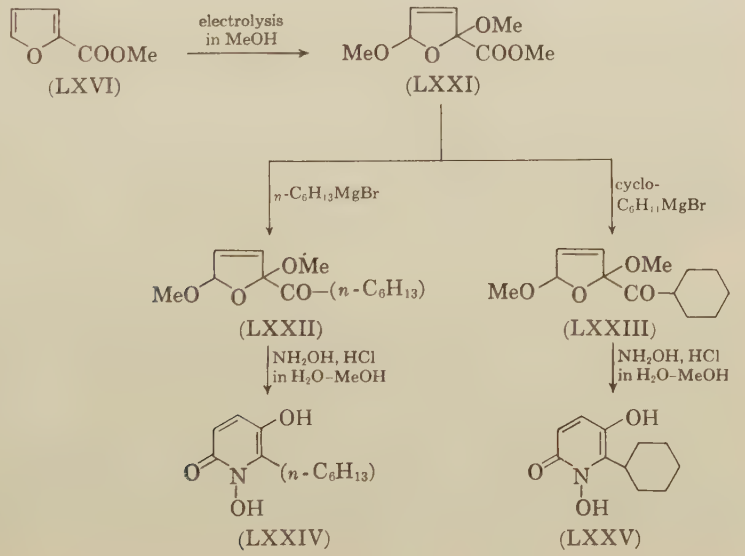
LXVIII has been used in a new synthesis of 3-hydroxy-2-piperidone (41).

(*c*) *Cyclic Hydroxamic Acids.* 2-Acetylfuran (LIV) has been transformed into 1,5-dihydroxy-6-methyl-2-pyridone (LXX) (89,90).

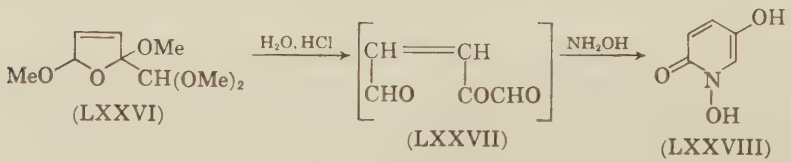


LIV was first methoxylated via its dimethyl ketal. Reaction with an aqueous solution of hydroxylamine hydrochloride yielded LXX, the reaction apparently involving the reactive intermediate LXIX or its equivalent.

By similar reactions 1,5-dihydroxy-6-(*n*-hexyl)-2-pyridone (LXXIV) and 1,5-dihydroxy-6-cyclohexyl-2-pyridone (LXXV) were prepared from methyl furoate (LXVI). LXVI was first methoxylated to LXXI, from which the two ketones (LXXII) and (LXXIII) were obtained (90).

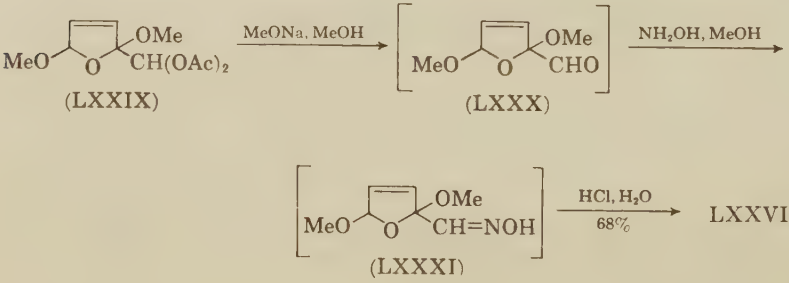


The unsubstituted hydroxamic acid 1,5-dihydroxy-2-pyridone (LXXVIII) has also been prepared, though under somewhat different reaction conditions (90). One might expect any easily hydrolyzable derivative of 2-*cis*-pentene-1,5-dial-4-one (LXXVII) to react with hydroxylamine hydrochloride to give LXXVIII. 2,5-Dimethoxy-2-dimethoxymethyl-2,5-dihydrofuran (LXXVI) gave, however, only a dark reaction mixture, from which no LXXVIII could be isolated. The mixture nevertheless gave a strong violet ferric chloride reaction indicating that a small amount of LXXVIII actually was formed.



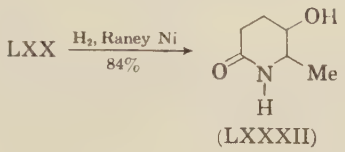
(LXXVI) (LXXVII) (LXXVIII)

A good yield of LXXVIII was obtained by using 2,5-dimethoxy-2,5-dihydrofurfural (LXXX) as a starting material. A methanolic solution of LXXX was prepared from 2,5-dimethoxy-2-diacetoxymethyl-2,5-dihydrofuran (LXXIX), the solution treated with hydroxylamine and the reaction product hydrolyzed and condensed to yield LXXVIII. The reaction probably proceeds through the oxime LXXXI or its equivalent, the initial attachment of the hydroxylamine to the organic molecule thus taking place at one of the ends of the chain of carbon atoms as required for the formation of LXXVIII.

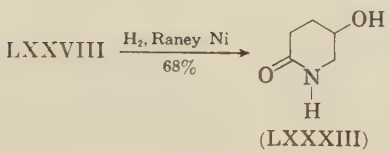


(LXXIX) (LXXX) (LXXXI)

LXX and LXXVIII have been catalytically hydrogenated to 5-hydroxy-6-methyl-2-piperidone (LXXXII) and 5-hydroxy-2-piperidone (LXXXIII), respectively (89,90).

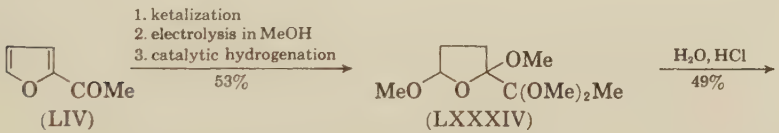


(LXXXII)



(LXXXIII)

(*d*) *Benzenoid Compounds.* Transformation of furans into benzenoid compounds has been accomplished in a number of ways. 2-Acetylfuran (LIV) has been used as a starting material for the following synthesis of pyrocatechol (LXXXVI) (89).



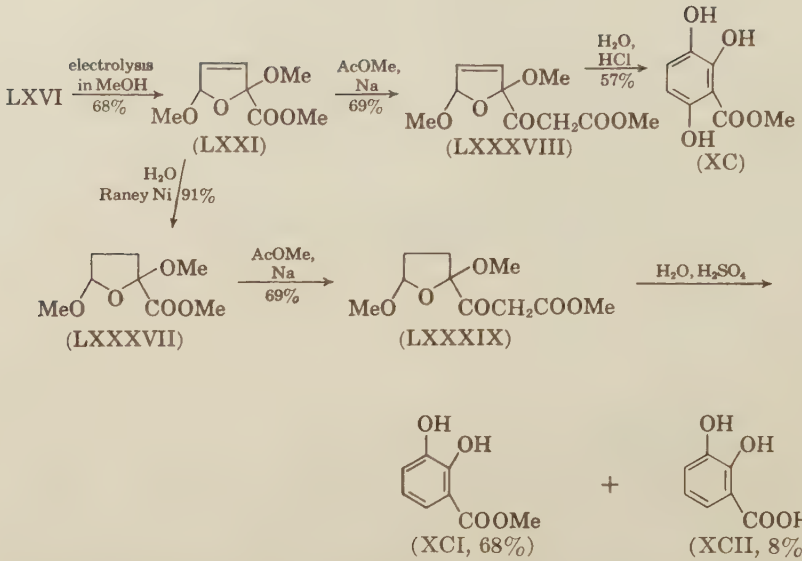
(LIV) (LXXXIV)

(LXXXV) (LXXXVI)

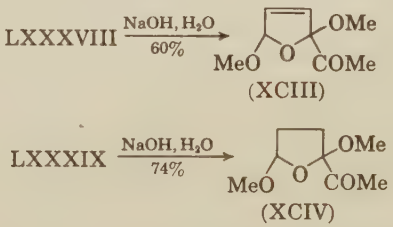
Evidently, hydrolysis of LXXXIV to hexane-4,5-dione-1-al (LXXXV) followed by intramolecular condensation takes place.

From methyl furoate (LXVI) the methyl esters of 2,3-dihydroxybenzoic acid (XCI) and of 2,3,6-trimethoxybenzoic acid (XC) have been prepared by the reactions shown below (29). A small amount of the free 2,3-dihydroxybenzoic acid (XCII) was also isolated.

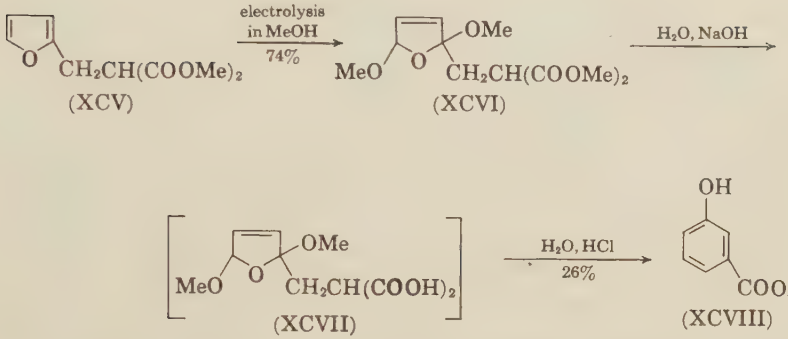
From the reaction scheme it is seen that ester condensations of LXXI and LXXXVII to furnish LXXXVIII and LXXXIX, respectively, have been involved. In this connection, it is of interest to



note that the β-keto ester groups of LXXXVIII and LXXXIX undergo ketonic hydrolysis, and the two ketones XCIII and XCIV have been isolated (42).

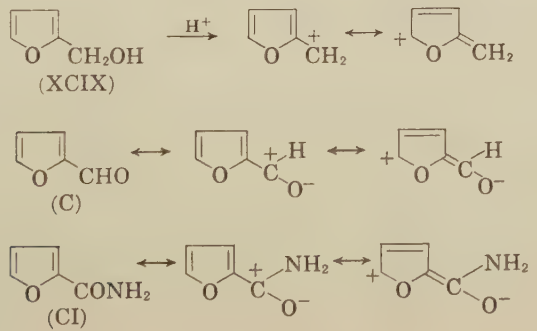


Investigations aimed at the preparation of tropolones from furans with suitable side chains in the 2-position (such as 2-(α-oxo-γ,γ-(dicarbomethoxy)propyl)furan, cf. 42) have so far been unsuccessful (49). As a model experiment for a possible synthesis of 4-tropolone carboxylic acid, however, *m*-hydroxybenzoic acid (XCVIII) was prepared from 2-(β,β-dicarbomethoxyethyl)furan (XCV) (40). XCV was electrolytically methoxylated to XCVI. Alkaline hydrolysis gave a solution of XCVII, and the reaction mixture was then treated with dilute hydrochloric acid. *m*-Hydroxybenzoic acid (XCVIII) was isolated in a 26% yield.



(*e*) *Direct Transformation of Furans into Pyridinols.* The methods described above for the transformation of furans into other systems with aromatic character all involve an oxidation step, that is, an alkoxylation, for the preparation of the desired intermediate undergoing intramolecular condensation. Since it is possible to transform certain furans directly into pyridinols, it seems justified to mention briefly the following reactions of this type, even though they do not involve dialkoxydihydrofurans as intermediates.

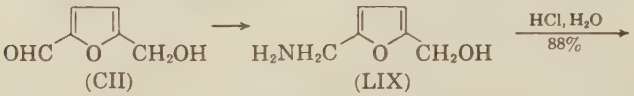
It is known that certain furans under special conditions are able to form *cis*-1,4-dicarbonyl systems without oxidation (cf. 35). The furans in question are those 2-substituted derivatives which are able to yield a carbonium ion on the α-carbon atom in the side chain. Examples (furfuryl alcohol (XCIX), furfural (C), and furoic acid amide (CI)) are shown below. The formation of the dicarbonyl system by displacement of charge appears from the mesomeric formulas shown (cf. 11a).

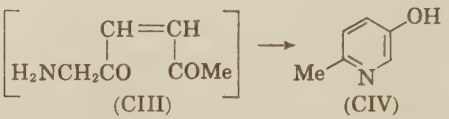


Reactions of this type have been utilized for the direct transformation of furans into pyridinols.

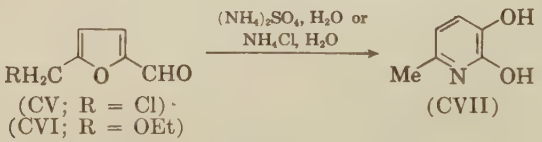
By interaction with alcoholic ammonia, furfural gives 3-pyridinol in low yield (61). Many reactions of this type have been carried out in varying yields (36,62,77–79,95).

6-Methyl-3-pyridinol (ClV) has been prepared in high yield from 2-(hydroxymethyl)-5-(aminomethyl)furan (LIX) (obtained from 5-(hydroxymethyl)furfural (CII)) and the transformation is assumed to take place through the dicarbonyl compound (CIII) (48).





Interaction of an aqueous solution of ammonium sulfate or chloride and derivatives of CII (such as CV and CVI) gives 6-methyl-2,3-pyridinediol (CVII) (1). The yields were not reported, but were probably about 1%.



Boiling furoic acid amide (CI) with hydrochloric acid has been reported to give 2,3-pyridinediol (LXVIII) in low, unspecified yield. 5-Methylfuroic acid amide (CVIII) reacts similarly when heated with sulfuric acid (2).

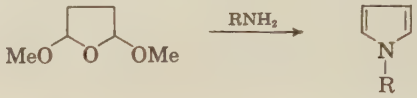
8. Transformation of Furans into Pyrroles

Yur'ev *et al.* (for references see 46) have described a method for transforming a furan into the corresponding pyrrole or *N*-substituted

TABLE IX
Synthesis of Pyrroles from 2,5-Dimethoxytetrahydrofurans

Starting material	RNH_2 compound	Reaction product	Yield, %	Ref.
2,5-Dimethoxytetrahydrofuran	Ammonia	Pyrrole	53	46
2,5-Dimethoxytetrahydrofuran	*n*-Butylamine	1-*n*-Butylpyrrole	28	46
2,5-Dimethoxytetrahydrofuran	*n*-Amylamine	1-*n*-Amylpyrrole	37	46
2,5-Dimethoxytetrahydrofuran	Aniline	1-Phenylpyrrole	78	46
2,5-Dimethoxytetrahydrofuran	*o*-Toluidine	1-*o*-Tolylpyrrole	71	46
2,5-Dimethoxytetrahydrofuran	*p*-Phenylenediamine	1,1′-*p*-Phenylenedipyrryl	41	46
2,5-Dimethoxy-2-methyltetrahydrofuran	Ammonia	2-Methylpyrrole	37	46
2,5-Dimethoxy-2-methyltetrahydrofuran	Aniline	1-Phenyl-2-methylpyrrole	77	46
2,5-Dimethoxy-2-(acetamidomethyl)tetrahydrofuran	*n*-Amylamine	1-*n*-Amyl-2-(acetamidomethyl)pyrrole	75	46
2,5-Dimethoxy-2-(acetamidomethyl)tetrahydrofuran	Aniline	1-Phenyl-2-(acetamidomethyl)-pyrrole	88	31
2,5-Dimethoxy-2-(methoxymethyl)tetrahydrofuran	Aniline	1-Phenyl-2-(methoxymethyl)pyrrole	22	46
2,5-Dimethoxy-2-(dimethoxymethyl)tetrahydrofuran	Ammonia	2-Pyrrolecarboxaldehyde	32	46
2,5-Dimethoxy-2-(dimethoxymethyl)tetrahydrofuran	Aniline	1-Phenyl-2-pyrrolecarboxaldehyde	46	46
2,5-Dimethoxy-2-(carbomethoxy)tetrahydrofuran	Ammonia	Methyl 2-pyrrolecarboxylate	17	46
2,5-Dimethoxy-2-(carbomethoxy)tetrahydrofuran	Aniline	Methyl 1-phenyl-2-pyrrolecarboxylate	57	46
2,5-Dimethoxy-3-isopropyltetrahydrofuran	Aniline	1-Phenyl-3-isopropylpyrrole	83	46
2,5-Dimethoxy-2-carbomethoxy-5-(*tert*-butyl)-tetrahydrofuran	Aniline	1-Phenyl-2-carbomethoxy-5-(*tert*-butyl)pyrrole	57	87

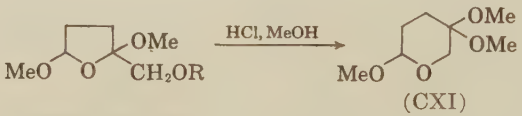
pyrrole by passing the furan and a large excess of ammonia or an amine, in the vapor phase, over aluminum oxide at about 400°. A simpler and more versatile method for transforming furans into pyrroles, giving higher yields, has been accomplished by way of 2,5-dimethoxytetrahydrofurans (31,46,87), and this reaction can also be applied in the case of furans, which cannot be successfully brought into the vapor phase.



The reaction between the 2,5-dimethoxytetrahydrofuran and ammonia or an amine is usually carried out in acetic acid, but some pyrroles have also been prepared in the liquid phase without a solvent or in the vapor phase over aluminum oxide. Table IX lists pyrroles synthesized from furans by this method.

9. Synthesis of 2,5,5-Trimethoxytetrahydropyran

When 2,5-dimethoxy-2-hydroxymethyltetrahydrofuran (CIX) or 2,5-dimethoxy-2-acetoxymethyltetrahydrofuran (CX) was heated under reflux with methanolic hydrogen chloride, a new compound was formed, which was shown to be 2,5,5-trimethoxytetrahydropyran (CXI) (12). The yields were 69 and 73%, respectively.

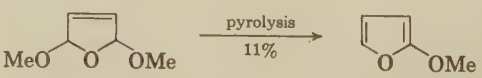


(CXI)

(CIX; R = H)
(CX; R = Ac)

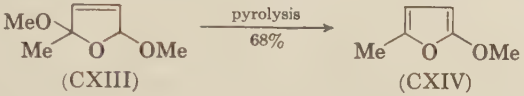
10. Pyrolysis of 2,5-Dialkoxy-2,5-dihydrofurans

Cava, Wilson, and Williams (3) heated a solution of 2,5-dimethoxy-2,5-dihydrofuran (II) in *n*-butyl phthalate containing a small amount of β-naphthalene sulfonic acid to 360° during 2 hr. and thereby obtained 2-methoxyfuran (CXII). The yield was 11%.



(II) (CXII)

Sherman and Dunlop (103) similarly subjected 2,5-dimethoxy-2-methyl-2,5-dihydrofuran (CXIII) to acid-catalyzed pyrolysis whereby 5-methoxy-2-methylfuran (CXIV) (68%) and methanol (64%) were formed together with trimethyl ortholevulinate (5–6%) and an unidentified polymer (about 13% by weight).



(CXIII) (CXIV)

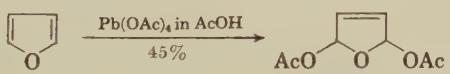
D. POTENTIAL APPLICATIONS OF 2,5-DIALKOXY-2,5-DIHYDROFURANS

The many reactions of the dialkoxydihydrofurans show that these compounds represent useful intermediates for synthetic organic chemistry. It is evident that the reactions published so far constitute only a few of the many conceivable applications of these compounds and it is clear that by varying the substituents of the dialkoxydihydrofurans, and the nature of their reaction partners in intermolecular condensations, a wealth of reactions can be devised. As examples of suggested possibilities for possible exploration, the following may be mentioned: syntheses of certain carbohydrates from dihydroxydialkoxytetrahydrofurans, syntheses of tropolones, hydroxytropolones or carboxytropolones and syntheses of new heterocyclic ring systems, e.g., azatropolones (cf. 28,42). It is to be hoped that further basic research in this area will reveal still other synthetic potentialities for these versatile dialkoxydihydrofuran intermediates not only for the solution of specific synthetic problems but also for the preparation of new classes of compounds and of new aromatic and heterocyclic ring systems.

III. 2,5-Diacyloxy-2,5-dihydrofurans

A. PREPARATION

When furan (I) is treated with lead tetraacetate in acetic acid, 1,4-addition takes place and 2,5-diacetoxy-2,5-dihydrofuran (CXV) is formed (5).



(I) (CXV)

This method of preparation has been simplified by using red lead oxide without isolating the lead tetraacetate (44). The yield was 69%. Extension of the method has led to the syntheses of 2,5-dipropionoxy-, 2,5-dibutyroxy-, and 2,5-dibenzoxy-2,5-dihydrofuran (44) and 2,5-diacetoxy-3-isopropyl-2,5-dihydrofuran (39). The acetoxylation of some 2-substituted furans (2-methylfuran, furfuryl acetate, furfural diacetate, and 2-acetylfuran) has been attempted, but without success, as no pure compounds could be isolated (39). The reaction between 2,5-diarylfurans and lead tetraacetate in chloroform and in acetic acid has been extensively studied by Dien and Lutz (33). With these furans several oxidation paths are involved. No 2,5-diacetoxy-2,5-dihydrofurans were isolated, but in some cases *cis* unsaturated 1,4-diketones were obtained.

Another synthesis of CXV consists of the action of bromine on furan in acetic acid containing potassium acetate (6). Special precautions must be taken since even traces of hydrogen bromide or hydrogen bromide-forming by-products cause destruction of the very acid sensitive diacetoxydihydrofuran (23). The lead salt method, however, gives halogen free, stable products.

B. *CIS-TRANS* ISOMERISM

2,5-Diacetoxy-2,5-dihydrofuran, prepared by the lead salt method, is usually obtained as a liquid, but has been found to consist one-third of a crystalline isomer and two-thirds of another isomer, which could not be obtained in crystalline form (44). The two isomers were separated by crystallization from methanol. It was shown by hydrolysis and identification of malealdehyde that both compounds actually were 2,5-diacetoxy-2,5-dihydrofuran. They must therefore be *cis-trans* isomers. It was not determined which of the compounds was the *cis* and which the *trans* isomer. Since the *trans* isomer is a racemic form, attempts have been made to resolve the two isomers. Chromatography on *d*-lactose according to the method of Prelog and Wieland (93) was, however, unsuccessful (43). 2,5-Diacetoxy-2,5-dihydrofuran, prepared by the bromine method, also crystallized readily from methanol and has been found to consist about half of the crystalline isomer (44). It is quite reasonable that the two *cis-trans* isomers are formed in different proportions by the two different methods of preparation. 2,5-Dipropionoxy-2,5-dihydrofuran was, like

2,5-diacetoxy-2,5-dihydrofuran, found to consist of a liquid and a crystalline isomer (in proportion of about 1 : 3), which were shown to be *cis-trans* isomers by hydrolysis and identification of malealdehyde. 2,5-Dibutyroxy-2,5-dihydrofuran seems to consist almost entirely of either the *cis* or the *trans* isomer, whereas 2,5-dibenzoxy-2,5-dihydrofuran appears to be a mixture of the *cis* and the *trans* isomer (44).

C. REACTIONS

1. Hydrogenation: 2,5-Diacyloxytetrahydrofurans

2,5-Diacetoxy-2,5-dihydrofuran (CXV) may, similar to 2,5-dimethoxy-2,5-dihydrofuran, be hydrogenated catalytically to the corresponding 2,5-diacetoxytetrahydrofuran (23). The rate of hydrogenation is much slower than in the case of the dialkoxy compound, and the course of the reaction largely depends on the purity of CXV. With bromine-containing CXV, good yields of 2,5-diacetoxytetrahydrofuran were obtained in some experiments, whereas other experiments led to the formation of lower boiling compounds such as acetic acid and succinaldehyde. Sometimes no hydrogenation at all took place. Reproducible results were first achieved when bromine-free CXV—best prepared by the lead salt method—was used for the hydrogenation. 2,5-Dipropionoxy-, 2,5-dibutyroxy-, and 2,5-dibenzoxy-2,5-dihydrofuran have also been catalytically hydrogenated, and pure isomers of 2,5-diacetoxy- and 2,5-dipropionoxytetrahydrofuran have been prepared (44).

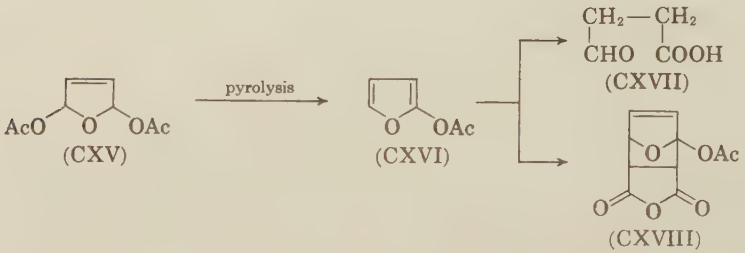
2. Hydrolysis

The 2,5-diacyloxy-2,5-dihydrofurans and the 2,5-diacyloxytetrahydrofurans can, like the dialkoxy compounds, be hydrolyzed by acids to give malealdehyde and succinaldehyde, respectively, but, contrary to the dialkoxy compounds, they are unstable under alkaline conditions. Reactions of the kind described for the dialkoxy compounds, that is, acid hydrolysis followed by intermolecular condensation of the 1,4-dicarbonyl compounds with various substances, can also be carried out with diacyloxy compounds, but the fact that only furan itself and 3-isopropylfuran have been acyloxylated has limited the application of these reactions.

Acid hydrolysis of CXV followed by condensation with hydrazine yielded pyridazine (85%) (23).

3. Pyrolysis of 2,5-Diacetoxy-2,5-dihydrofuran: Reactions with 2-Acetoxyfuran

By pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran (CXV) at 480–500° under 10 mm., acetic acid is split off and 2-acetoxyfuran (CXVI) is formed (13).

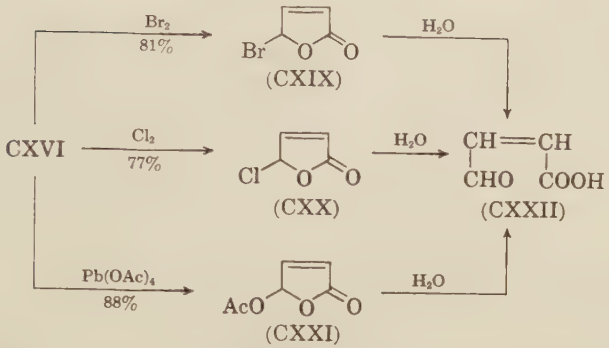


CXVI reacts with dinitrophenylhydrazine in 2*N* aqueous hydrochloric acid to give the dinitrophenylhydrazone of β-formylpropionic acid (CXVII), and with maleic anhydride it forms an addition product (CXVIII). The course of the pyrolysis depends upon the quality of CXV. CXV, prepared by the lead salt method, gave a 35% yield of CXVI. Pyrolysis of CXV, prepared by the bromine method, has also given about 35% of CXVI, but the yield was often considerably lower and at the same time varying amounts of γ-hydroxycrotonolactone were formed. Higher yields in the pyrolysis have been reported by Cava, Wilson, and Williams (3,4) who obtained an 81% yield of CXVI by conducting the cracking of CXV in the liquid phase at 160–190° in the presence of a catalytic amount of acid.

β-Formylpropionic acid (CXVII), which can be obtained by acid hydrolysis of CXVI, is an important synthetic intermediate, which has been applied by Fox and Bullock (58) in their modification of Ellinger's (37) preparation of 3-indoleacetic acid by the Fischer indole synthesis.

CXVI reacts with bromine and chlorine to form 2-oxo-5-bromo-2,5-dihydrofuran (CXIX) and 2-oxo-5-chloro-2,5-dihydrofuran (CXX), respectively, and with lead tetraacetate in acetic acid to give 2-oxo-5-acetoxy-2,5-dihydrofuran (CXXI) (45).

The three compounds CXIX, CXX, and CXXI were all hydrolyzed to *cis*-β-formylacrylic acid (CXXII).



4. Transformation of 2,5-Diacetoxy-2,5-dihydrofuran into 2,3,5-Trimethoxytetrahydrofuran and into 2,5-Diacetoxy-3-chloro-4-hydroxytetrahydrofuran

Stoll, Lindenmann, and Jucker (111) reported the transformation of 2,5-diacetoxy-2,5-dihydrofuran (CXV) into 2,3,5-trimethoxytetrahydrofuran. CXV was dissolved in anhydrous methanol containing 2% of hydrogen chloride and the reaction mixture left standing at 20° for 1 hr. followed by heating under reflux for 3 hr. 2,3,5-Trimethoxytetrahydrofuran was isolated in almost quantitative yield.

Like the dialkoxydihydrofurans (see Section II-C-4), 2,5-diacetoxy-2,5-dihydrofuran (CXV) adds hypochlorous acid to the 3,4-double bond (104). When CXV was treated with *tert*-butyl hypochlorite in acetic acid, 2,5-diacetoxy-3-chloro-4-hydroxytetrahydrofuran was isolated in 97% yield.

IV. Experimental

A. 2,5-DIMETHOXY-2,5-DIHYDROFURAN (27)

Apparatus. Figure 1 gives a detailed design of the cell used for the electrolysis. The cathode consists of two brass cylinders electroplated with nickel, while the anode is a porcelain tube covered with sheet platinum. During electrolysis the electrolyte circulates continuously owing to the evolution of hydrogen at the inner surface of the inner cathode.

The cell is fed from a storage battery or from a rectifier and is connected with an ammeter and a coulometer of the ordinary domestic type.

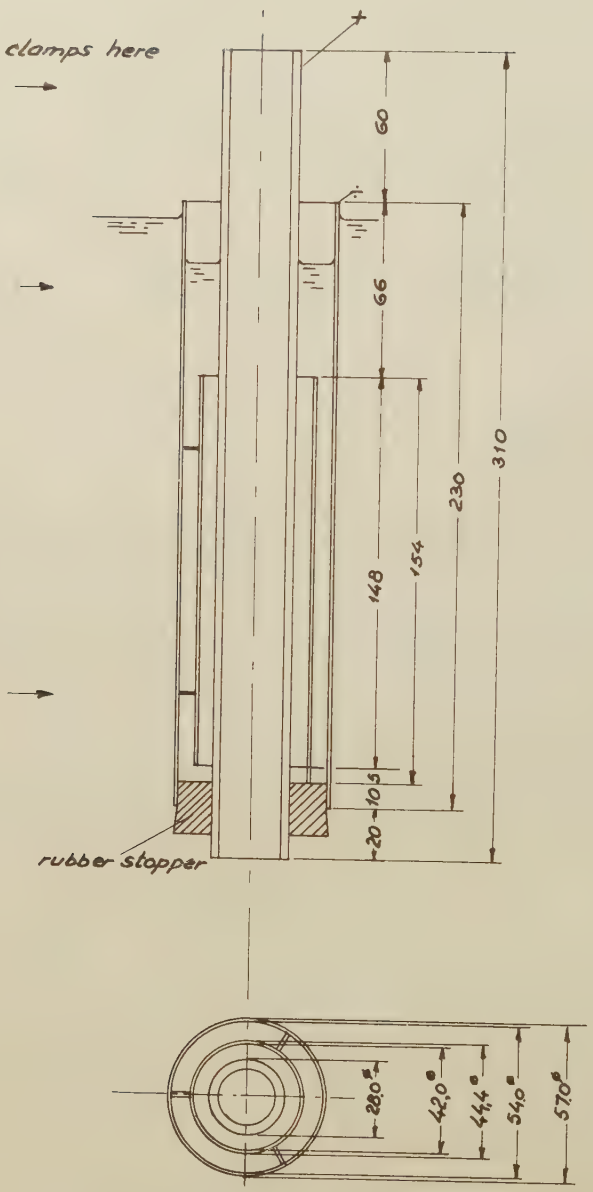


Fig. 1. Cell for electrolytic alkoxylations.

Procedure. 5.00 g. of ammonium bromide (0.051 mole) is dissolved in a mixture of 230 ml. of methanol (5.7 moles) and 68.0 g. of furan (1.00 mole) and the solution (total volume about 310 ml.) poured into the cell. The cell is placed in a cooling bath kept at −22° and the voltage applied after some minutes. The data of the electrolysis are given in Table X.

TABLE X

Hours	Current, amp.	Potential across the cell during electrolysis, v.	Temperature in the cell, °C.	Ampere hours	Per cent of theoretical amount
0.3	3.0	4.6	−14	1.0	2
5.8	3.0	4.8	−14	10.9	20
7.9	3.0	4.8	−14	23.6	44
15.5	2.4	5.2	−14	44.7	83
15.9	2.3	5.3	−14	45.6	85

After 45.6 ampere hours have passed through the cell (85% of the theoretical amount), the electrolysis is stopped. The volume of the liquid in the cell has diminished by 35 ml., mainly due to contraction. The liquid, which is colorless in the upper part of the cell but slightly yellow from unreacted bromine near the bottom, is poured into a solution of sodium methoxide (1.20 g. of sodium (0.052 mole) in 20 ml. of methanol) and the mixture distilled through a Vigreux column from a water bath under atmospheric pressure. About 160 ml. of distillate, containing ammonia and the excess furan, is collected. The residue

TABLE XI

Fraction	Weight, g.	B. p., °C.	n_D^{25}	OCH_3, % (calc. 47.7%)
1	2	80–160		
2	26.4	160	1.4321	47.8
3	25.4	160–161	1.4323	47.1
4	24.3	161	1.4322	47.5
5	19.3	161–162	1.4326	46.9
Residue	5			

consists of a clear yellowish brown liquid and a precipitate of sodium bromide, which is filtered off and washed with a little ether. The filtrate is then distilled through a 5 cm. packed column (21).

All fractions show a negative Beilstein test for halogens. The yield of 2,5-dimethoxy-2,5-dihydrofuran from fractions 2–5 was 95.4 g. (73%); the current efficiency was 86%.

B. 2,5-DIMETHOXYTETRAHYDROFURAN (23)

50.0 g. of analytically pure 2,5-dimethoxy-2,5-dihydrofuran and 60 ml. of methanol (technical product) are shaken with 1.5 g. of Raney nickel under 100 atm. for 1 hr. The temperature rises to about 80° during the first few minutes of shaking. After hydrogenation, the methanol is removed through a 5 cm. packed column (21) and the residue distilled under ordinary pressure without the column.

TABLE XII

Fraction	Weight, g.	B. p., °C.	n_D^{25}
1	2.6	145.2–147.2	1.4138
2	40.4	147.2–149.6	1.4160
3	3.3	148.0–152.0	1.4160
4	1.2	151.3–160.2	1.4160

It will be seen that the boiling point is not constant during the distillation, whereas the refractive index remains constant. In separate experiments it has been found that this is due to overheating which always occurs when the substance is distilled in the usual way without a column.

The yield of 2,5-dimethoxytetrahydrofuran from fractions 2–4 was 44.9 g. (89%).

C. TROPINONE (50,50a; cf. 59)

39.6 g. of 2,5-dimethoxytetrahydrofuran (0.30 mole) is dissolved in 240 ml. of water; 24 ml. of hydrochloric acid (1*N*) is added and the mixture heated under reflux for 30 min. The pale yellow solution is cooled, neutralized with 24 ml. of a 1*N* solution of sodium hydroxide, and added to a solution of 88.2 g. of acetonedicarboxylic acid (0.60 mole), 40.5 g. of methylamine hydrochloride (0.60 mole), and 185 g. of sodium acetate in 500 ml. of water. The mixture is heated and kept at

55–60° for 90 min. After cooling, 90 g. of potassium carbonate and 125 g. of sodium chloride are dissolved in the reaction mixture and the solution extracted with 4 × 200 ml. of ether and then continuously with ether overnight. The ethereal extract is dried over magnesium sulfate and distilled. The yield is 34.0 g. (81%) of tropinone ($b.p._{14}$ 105–108°, m.p. 41–42°, Hershberg apparatus, corr.).

D. 2,5-DIACETOXY-2,5-DIHYDROFURAN (44)

580 ml. of glacial acetic acid and 230 ml. of acetic anhydride are placed in a 1-liter three-necked flask provided with a stirrer, a thermometer, and a reflux condenser with a calcium chloride tube. 300 g. of red lead oxide (0.44 mole) is added to the stirred solution in portions of 15–20 g. The temperature is kept at 50° by external heating. The addition takes about $3^1/_2$ hr. and part of the lead tetraacetate formed precipitates as white crystals. 29.8 g. of furan (0.44 mole) is added, the temperature raised to 60°, and heating discontinued. In the course of the following 10 min. the temperature rises to 65°. The reaction mixture is then kept at 60–65° for 75 min., first by occasional cooling, later by external heating. The mixture is now a clear, pale yellow solution. The major part of the solvent is distilled under 10 mm. from a water bath of 60–65°, and 400 ml. of anhydrous ether is added to the pasty residue. The mixture is shaken for some minutes and then stirred vigorously, whereby the precipitate becomes readily filterable. The lead acetate is filtered off on a sintered glass disk and washed with 100 ml. of anhydrous ether to give 415 g. (97%).

The yellowish brown filtrate is distilled from a water bath maintained at 70°, and finally *in vacuo*, and the residue distilled further *in vacuo*. After 15–20 g. of a pale yellow fore-run ($b.p._{10}$ <127°), the main fraction is collected. 2,5-Diacetoxy-2,5-dihydrofuran (56.0 g., 69%) is obtained as a pale yellow liquid ($b.p._{0.5}$ 89–93°, n_D^{25} 1.4536). The color does not disappear on redistillation.

Acknowledgment. The author is indebted to A/S Sadolin & Holmblad, Copenhagen, Denmark, for permission to refer to unpublished work from its research laboratories.

References

1. Aso, K., *J. Agr. Chem. Soc. Japan, 16*, 249 (1940); *Chem. Abstr., 34*, 6278 (1940).
2. Aso, K., *J. Agr. Chem. Soc. Japan, 16*, 253 (1940); *Chem. Abstr., 34*, 6940 (1940).
3. Cava, M. P., C. L. Wilson, and C. J. Williams, *Chem. & Ind., 1955*, 17.
4. Cava, M. P., C. L. Wilson, and C. J. Williams, *J. Am. Chem. Soc., 78*, 2303 (1956).
5. Clauson-Kaas, N., *Kgl. Danske Videnskab. Selskab, Mat.-fys. Medd., 24*, No. 6 (1947).
6. Clauson-Kaas, N., *Acta Chem. Scand., 1*, 379 (1947).
7. Clauson-Kaas, N., *Acta Chem. Scand., 6*, 556 (1952).
8. Clauson-Kaas, N., *Acta Chem. Scand., 6*, 569 (1952).
9. Clauson-Kaas, N., Danish Pat. 78,381 (Nov. 8, 1954) (to A/S Sadolin & Holmblad).
10. Clauson-Kaas, N., U. S. Pat. 2,748,147 (May 29, 1956) (to A/S Sadolin & Holmblad).
11. Clauson-Kaas, N., Danish Pat. 78,714 (Jan. 10, 1955) (to A/S Sadolin & Holmblad).

11a. Clauson-Kaas, N., *Nord Kemikermøde, 9, Aarhus 1956, II*, 149–156; *Chem. Abstr., 52*, 7267 (1958).

12. Clauson-Kaas, N., P. Dietrich, and J. T. Nielsen, *Acta Chem. Scand., 7*, 845 (1953).
13. Clauson-Kaas, N., and N. Elming, *Acta Chem. Scand., 6*, 560 (1952).
14. Clauson-Kaas, N., and N. Elming, U. S. Pat. 2,806,852 (Sept. 17, 1957) (to A/S Sadolin & Holmblad).
15. Clauson-Kaas, N., and N. Elming, Unpublished work from A/S Sadolin & Holmblad, Copenhagen, Denmark.
16. Clauson-Kaas, N., N. Elming, and J. T. Nielsen, Belg. Pat. 543,155 (Dec. 15, 1955) (to A/S Sadolin & Holmblad).
17. Clauson-Kaas, N., N. Elming, and Z. Tyle, *Acta Chem. Scand., 9*, 1 (1955).
18. Clauson-Kaas, N., and J. Fakstorp, *Acta Chem. Scand., 1*, 415 (1947).
19. Clauson-Kaas, N., and F. Limborg, *Acta Chem. Scand., 1*, 619 (1947).
20. Clauson-Kaas, N., and F. Limborg, *Acta Chem. Scand., 6*, 551 (1952).
21. Clauson-Kaas, N., and F. Limborg, *Acta Chem. Scand., 8*, 1579 (1954).
22. Clauson-Kaas, N., F. Limborg, and P. Dietrich, *Acta Chem. Scand., 6*, 545 (1952).
23. Clauson-Kaas, N., S.-O. Li, and N. Elming, *Acta Chem. Scand., 4*, 1233 (1950).
24. Clauson-Kaas, N., F. Limborg, and N. Elming, Unpublished work from A/S Sadolin & Holmblad, Copenhagen, Denmark.
25. Clauson-Kaas, N., F. Limborg, N. Elming, and P. Nedenskov, Unpublished work from A/S Sadolin & Holmblad, Copenhagen, Denmark.
26. Clauson-Kaas, N., F. Limborg, and J. Fakstorp, *Acta Chem. Scand., 2*, 109 (1948).
27. Clauson-Kaas, N., F. Limborg, and K. Glens, *Acta Chem. Scand., 6*, 531 (1952).

28. Clauson-Kaas, N., and P. Nedenskov, *Acta Chem. Scand.*, *9*, 14 (1955).
29. Clauson-Kaas, N., and P. Nedenskov, *Acta Chem. Scand.*, *9*, 27 (1955).
30. Clauson-Kaas, N., J. T. Nielsen, and E. Boss, *Acta Chem. Scand.*, *9*, 111 (1955).
31. Clauson-Kaas, N., and Z. Tyle, *Acta Chem. Scand.*, *6*, 667 (1952).
32. Clauson-Kaas, N., and Z. Tyle, *Acta Chem. Scand.*, *6*, 962 (1952).
33. Dien, C.-K., and R. E. Lutz, *J. Org. Chem.*, *22*, 1355 (1957).
34. Dunlop, A. P., and F. N. Peters, *The Furans*, Reinhold, New York, 1953, pp. 50–52, 80–81, 142, 218–219, 385, 391–393.
35. Dunlop, A. P., and F. N. Peters, *The Furans*, Reinhold, New York, 1953, p. 646.
36. Dunlop, A. P., and F. N. Peters, *The Furans*, Reinhold, New York, 1953, pp. 667, 671.
37. Ellinger, A., *Ber.*, *37*, 1801 (1904).
38. Elming, N., *Acta Chem. Scand.*, *6*, 572 (1952).
39. Elming, N., *Acta Chem. Scand.*, *6*, 578 (1952).
40. Elming, N., *Acta Chem. Scand.*, *10*, 1664 (1956).
41. Elming, N., *Acta Chem. Scand.*, *11*, 914 (1957).
42. Elming, N., *Acta Chem. Scand.*, *11*, 1493 (1957).
43. Elming, N., Unpublished work from A/S Sadolin & Holmblad, Copenhagen, Denmark.
44. Elming, N., and N. Clauson-Kaas, *Acta Chem. Scand.*, *6*, 535 (1952).
45. Elming, N., and N. Clauson-Kaas, *Acta Chem. Scand.*, *6*, 565 (1952).
46. Elming, N., and N. Clauson-Kaas, *Acta Chem. Scand.*, *6*, 867 (1952).
47. Elming, N., and N. Clauson-Kaas, *Acta Chem. Scand.*, *9*, 23 (1955).
48. Elming, N., and N. Clauson-Kaas, *Acta Chem. Scand.*, *10*, 1603 (1956).
49. Elming, N., and N. Clauson-Kaas, Unpublished work from A/S Sadolin & Holmblad, Copenhagen, Denmark.
50. Elming, N., and P. Nedenskov, Unpublished work from A/S Sadolin & Holmblad, Copenhagen, Denmark.
50a. Elming, N., and P. Nedenskov, Brit. Pat. 791,770 (March 12, 1958) (to A/S Sadolin & Holmblad).
51. Fakstorp, J., D. Raleigh, and L. E. Schniepp, *J. Am. Chem. Soc.*, *72*, 869 (1950).
52. Findlay, S. P., *J. Org. Chem.*, *22*, 1385 (1957).
53. Fodor, G., *Tetrahedron*, *1*, 86 (1957).
54. Fodor, G., *Acta Chim. Acad. Sci. Hung.*, *5*, 379 (1955).
55. Fodor, G., *Experientia*, *11*, 129 (1955).
55a. Fodor, G., in R. H. F. Manske, ed., *The Alkaloids*, Vol. VI, Academic Press, New York, 1960, pp. 145–77.
56. Fodor, G., J. Tóth, I. Koczor, P. Dobó, and I. Vincze, *Chem. & Ind.*, *1956*, 764.
57. Fodor, G., J. Tóth, I. Koczor, and I. Vincze, *Chem. & Ind.*, *1955*, 1260.
58. Fox, S. W., and M. W. Bullock, *J. Am. Chem. Soc.*, *73*, 2754 (1951).
59. Gál, G., I. Simonyi, and G. Tokár, *Acta Chim. Acad. Sci. Hung.*, *6*, 365 (1955)
60. Ginsburg, D., *Bull. Research Council Israel*, *2*, No. 3, 268 (1952).
61. Gruber, W., *Chem. Ber.*, *88*, 178 (1955).
62. Gruber, W., *Can. J. Chem.*, *31*, 564 (1953).
63. Gyermek, L., and K. Nádor, *J. Pharm. and Pharmacol.*, *9*, 209 (1957).

63a. Hardegger, E., and H. Furter, *Helv. Chim Acta, 40*, 872 (1957).
64. Heusner, A., *Arzneimittel-Forsch., 6*, 105 (1956).
65. Heusner, A., and K. Zeile, *Chem. Ber., 90*, 2114 (1957).
66. Hufford, D. L., D. S. Tarbell, and T. R. Koszalka, *J. Am. Chem. Soc., 74*, 3014 (1952).
67. Johnson, A. W., and H. N. Rydon, *Ann. Repts. on Progr. Chem., 47*, 222 (1950).
68. Jones, D. G., Brit. Pat. 595,041 (Nov. 25, 1947) (to Imperial Chemical Industries Ltd.).
69. Jones, D. G., Brit. Pat. 603,422 (June 15, 1948) (to Imperial Chemical Industries Ltd.).
70. Jones, D. G., Brit. Pat. 610,876 (Oct. 21, 1948) (to Imperial Chemical Industries Ltd.).
71. Jones, D. G., U. S. Pat. 2,515,304 (July 18, 1950) (to Imperial Chemical Industries Ltd.).
72. Jones, D. G., and A. W. C. Taylor, *Quart. Revs., 4*, 203 (1950).
73. Jucker, E., *Chimia, 9*, 195 (1955).
73a. Keagle. L. C., and W. H. Hartung, *J. Am. Chem. Soc., 68*, 1608 (1946).
74. Kebrle, J., and P. Karrer, *Helv. Chim. Acta, 37*, 484 (1954).
75. Kornfeld, E. C., *J. Org. Chem., 20*, 1135 (1955).
76. Krebs, H., J. A. Wagner, and J. Diewald, *Chem. Ber., 89*, 1875 (1956).
77. Leditschke, H., *Chem. Ber., 85*, 202 (1952).
78. Leditschke, H., *Chem. Ber., 86*, 123 (1953).
79. Leditschke, H., *Chem. Ber., 86*, 612 (1953).
80. Letsinger, R. L., and R. Lasco, *J. Org. Chem., 21*, 764 (1956).
81. Levisalles, J., *Bull. soc. chim. France, 1957*, 997.
82. Levisalles, J., and P. Baranger, *Compt. rend., 240*, 444 (1955).
83. Limborg, F., and N. Clauson-Kaas, *Acta Chem. Scand., 7*, 234 (1953).
83a. Marei, A. A., and R. A. Raphael, *J. Chem. Soc., 1958*, 2624.
84. Meinel, K., *Ann., 516*, 231 (1935).
85. Meinwald, J., S. L. Emerman, N. C. Yang, and G. Büchi, *J. Am. Chem. Soc., 77*, 4401 (1955).
85a. Murakami, M., S. Senoh, and Y. Hata, *Mem. Inst. Sci. Ind. Research Osaka Univ., 13*, 173 (1956); *Chem. Abstracts, 51*, 5745 (1957).
85b. Murakami, M., S. Senoh, and Y. Hata, *Proc. Japan. Acad., 32*, 135 (1956); *Chem. Abstr., 50*, 15504 (1956).
86. Nedenskov, P., and N. Clauson-Kaas, *Acta Chem. Scand., 8*, 1295 (1954).
87. Nedenskov, P., N. Elming, J. T. Nielsen, and N. Clauson-Kaas, *Acta Chem. Scand., 9*, 17 (1955).
88. Nielsen, J. T., N. Clauson-Kaas, and P. Dietrich, *Acta Chem. Scand., 9*, 182 (1955).
89. Nielsen, J. T., N. Elming, and N. Clauson-Kaas, *Acta Chem. Scand., 9*, 9 (1955).
90. Nielsen, J. T., N. Elming, and N. Clauson-Kaas, *Acta Chem. Scand., 9*, 30 (1955).
91. Nielsen, J. T., N. Elming, and N. Clauson-Kaas, *Acta Chem. Scand., 12*, 63 (1958).
92. Paul, R., *Bull. soc. chim. France, 1956*, 838.

92a. Potts, K. T., and R. Robinson, *J. Chem. Soc., 1955*, 2675.
93. Prelog, V., and P. Wieland, *Helv. Chim. Acta, 27*, 1127 (1944).
94. Preobrazhenskiĭ, N. A., I. A. Rubtsov, T. F. Dankova, and V. P. Pavlov, *J. Gen. Chem. (U.S.S.R.), 15*, 952 (1945); *Chem. Abstr., 40*, 6488 (1946).
95. Rapoport, H., and E. J. Volcheck, *J. Am. Chem. Soc., 78*, 2451 (1956).
96. Robinson, R., *J. Chem. Soc., 1917*, 762.
97. Rothlin, E., M. Täschler, H. Konzett, and A. Cerletti, *Experientia, 10*, 142 (1954).
98. Schmidt, C.-H., *Angew. Chem., 68*, 175 (1956).
99. Schöpf, C., and W. Arnold, *Ann., 558*, 109 (1947).
100. Schöpf, C., and G. Lehmann, *Ann., 518*, 1 (1935).
101. Schöpf, C., and A. Schmetterling, *Angew. Chem., 64*, 591 (1952).
102. Sheehan, J. C., and B. M. Bloom, *J. Am. Chem. Soc., 74*, 3825 (1952).
103. Sherman, E., and A. P. Dunlop, 127th Meeting, ACS, Cincinnati, Ohio, 1955, *Abstracts*, p. 6.
103a. Stern, R., and H. H. Wasserman, *J. Org. Chem., 24*, 1689 (1959).
104. Stoll, A., B. Becker, and E. Jucker, *Helv. Chim. Acta, 35*, 1263 (1952).
105. Stoll, A., and E. Jucker, *Chimia, 9*, 25 (1955).
106. Stoll, A., and E. Jucker, *Angew. Chem., 66*, 376 (1954).
107. Stoll, A., E. Jucker, and A. Ebnöther, *Helv. Chim. Acta, 38*, 559 (1955).
108. Stoll, A., E. Jucker, and A. Lindenmann, *Helv. Chim. Acta, 37*, 495 (1954).
109. Stoll, A., E. Jucker, and A. Lindenmann, *Helv. Chim. Acta, 37*, 649 (1954).
110. Stoll, A., E. Jucker, and A. Lindenmann, *Helv. Chim. Acta, 38*, 571 (1955).
111. Stoll, A., A. Lindenmann, and E. Jucker, *Helv. Chim. Acta, 36*, 1500 (1953).
112. Stoll, A., A. Lindenmann, and E. Jucker, *Helv. Chim. Acta, 36*, 1506 (1953).
113. van Tamelen, E. E., P. Barth, and F. Lornitzo, *J. Am. Chem. Soc., 78*, 5442 (1956).
114. Walker, J., *Ann. Repts. on Progr. Chem., 49*, 204 (1952).
115. Webb, J. S., U. S. Pat. 2,732,379 (Jan. 24, 1956) (to American Cyanamid Co.).
116. Weidlich, H., and W. Schulz, Ger. Pat. 956,946 (Jan. 24, 1957) (to C. H. Boehringer Sohn).
117. Williams, H., P. Kaufmann, and H. S. Mosher, *J. Org. Chem., 20*, 1139 (1955).
118. Wilson, W., *Ann. Repts. on Progr. Chem., 52*, 230 (1955).
119. Wohl, A., and B. Mylo, *Ber., 45*, 1746 (1912).
120. Zeile, K., and A. Heusner, *Chem. Ber., 90*, 1869 (1957).
121. Zeile, K., and A. Heusner, *Chem. Ber., 90*, 2800 (1957).
122. Zeile, K., and A. Heusner, *Chem. Ber., 90*, 2809 (1957).
123. Zeile, K., and A. Heusner, *Chem. Ber., 87*, 439 (1954).

ETHYNYL ETHERS AND THIOETHERS AS SYNTHETIC INTERMEDIATES

By J. F. ARENS, *The University of Groningen, Groningen, The Netherlands*

CONTENTS

I. Introduction 118
A. Scope of This Review 118
B. Historical Outline 118
II. Preparations and Properties 121
A. Preparation of Ethynyl Ethers 121
B. Properties of Ethynyl Ethers 126
C. Preparation of Ethynyl Thioethers and Their Derivatives 140
D. Properties of Ethynyl Thioethers 145
E. Preparation and Properties of Ethynylene Bisthioethers 145
F. Infrared Characteristics of Ethynyl Ethers and Thioethers 149
III. Reactions 151
A. General Outline of the Reactivity of Ethynyl Ethers and Thioethers 151
B. Reactions of the Ethynylic Hydrogen Atom 153
C. Preparation and Applications of Alkoxy- and (Alkylthio)ethynylcarbinols 157
D. Additions of Electrophilic Reagents to the Triple Bond 163
E. Additions of Nucleophilic Reagents to the Triple Bond 179
F. Free Radical Additions to the Triple Bond 186
G. Miscellaneous Reactions of the Triple Bond 189
H. Reactions Involving the Ether Group of Ethynyl Ethers 195
I. Reactions Involving the Thioether Group of Ethynyl Thioethers 199
J. Some Reagents Related to Ethynyl Ethers 200
IV. Experimental 202
A. Preparation of Ethoxyethyne 202
B. Preparation of an Ethoxyethynylcarbinol 203
C. Rearrangement of an Ethoxyethynylcarbinol into an α,β-Unsaturated Ester 204
D. Preparation of an α,β-Unsaturated Aldehyde from an Ethoxyethynylcarbinol 204
E. Preparation of a Dipeptide by Means of Ethoxyethyne 205
F. Preparation of an Acid Anhydride by Means of Ethoxyethyne 206
References 206

I. Introduction

A. SCOPE OF THIS REVIEW

Since 1940 ethynyl ethers of the type HC≡COR and their alkylated derivatives, R′C≡COR, have received considerable attention, largely because of their versatility as synthetic intermediates. More recently ethynyl thioethers have also been prepared and studied. This review covers both groups of compounds and includes relevant literature published up to mid-1959 as well as unpublished material from the author's laboratory.

The short historical survey and a review of the preparations of the compounds are followed by a general discussion of their reactions and of some well-established synthetic applications. Other uses, not yet fully explored, are outlined briefly. Theoretical discussions have been inserted at appropriate points. Detailed descriptions of some representative experimental procedures conclude the chapter.

B. HISTORICAL OUTLINE

The topics mentioned here will be discussed in more detail in the appropriate sections. Phenoxyethyne appears to be the first ethynyl ether to have been well described. The substance was obtained about 1900 by Slimmer (1) in Nef's laboratory by the following sequence of reactions.

$$CHBr{=}CHBr + C_6H_5ONa \longrightarrow C_6H_5OCH{=}CHBr + NaBr$$

$$C_6H_5OCH{=}CHBr + KOH \xrightarrow[\text{alcohol}]{\text{in}} C_6H_5OC{\equiv}CH + KBr + H_2O$$

An earlier claim of Sabanejeff and Dworkowitsch (2) to have prepared an ethynyl ether, viz., 1-bromo-2-phenoxyethyne, could not be substantiated (1).

In 1942 the first paper on ethynyl alkyl ethers describing a method for the preparation of ethoxy- and butoxyethyne was published by Jacobs, Cramer, and Hanson (3).

$$BrCH_2CH(OR)_2 \xrightarrow{Br_2} Br_2CHCH(OR)_2 \xrightarrow[\text{alcohol}]{Zn}$$

$$BrCH{=}CHOR \xrightarrow{KOH} HC{\equiv}COR$$

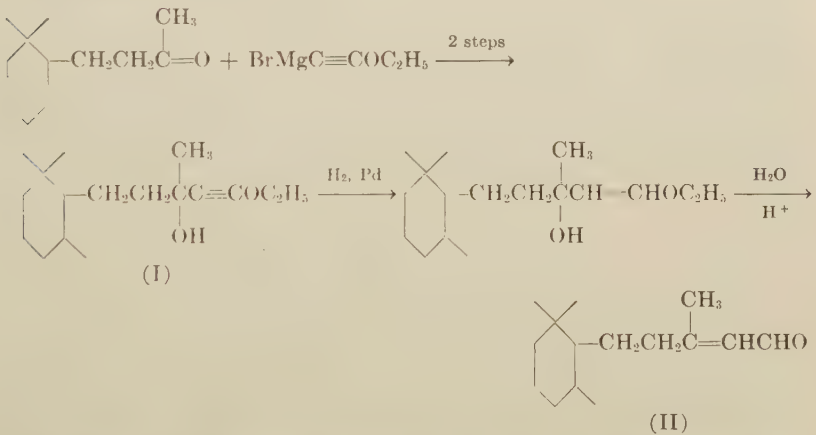
An earlier claim of the preparation of the sodium derivative of ethoxyethyne by Scheibler *et al.* (3a) is doubtful.

Ethynyl thioethers of the type HC≡CSR were not known prior to 1956, but at that time four independent reports were issued approximately simultaneously (3b–6).

Bis(arylthio)ethynes of the type RSC≡CSR, however, have been known since 1912 from the work of Fromm, Benzinger, and Schäfer (7). The first bis(alkylthio)ethyne was bis(*tert*-butylthio)ethyne, prepared by Backer and Strating in 1954 (8).

Bis(aryloxy)- and bis(alkoxy)ethynes, ROC≡COR, have not yet been described. Diethynyl ether, HC≡COC≡CH, diethynyl sulfide, HC≡CSC≡CH, and the corresponding ethynyl vinyl compounds are also unknown.

The first use of an ethynyl ether for a synthetic problem originated with Preobrazhenskiĭ and Shokina (9), who utilized ethoxyethyne for the synthesis of tetrahydro-β-ionylideneacetaldehyde (II). The ethoxyethynylcarbinol (I) was partially hydrogenated and then hydrolyzed by dilute acid.



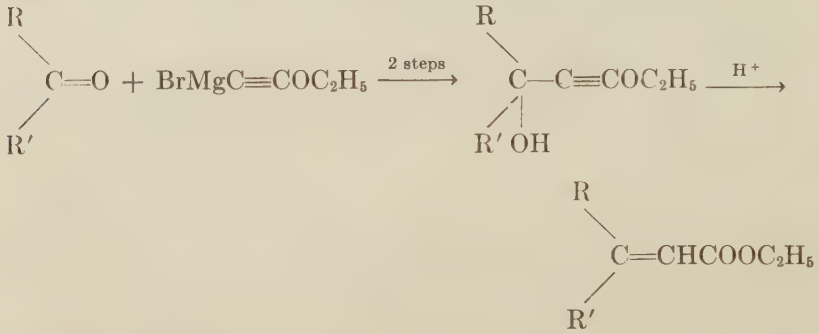
(I) (II)

Although this paper (9) was published in 1945,* it was unfortunately abstracted incorrectly by *Chemical Abstracts* (10), and as a result this method for the synthesis of α,β-unsaturated aldehydes remained unreported in the Western chemical literature. It was redeveloped

* According to a remark at the end of the paper (9), it had been submitted for publication for the first time in September, 1940, and for the second time in March, 1944. In 1940, however, ethoxyethyne was still unknown in the chemical literature, and the authors gave no reference as to its source, nor did they describe its preparation.

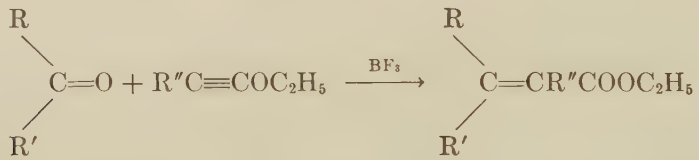
in 1947 by van Dorp and Arens (11) and applied to the synthesis of citral, β-ionylideneacetaldehyde, and vitamin A aldehyde (12).

In 1947, Shchukina and Rubtsov (13) used ethoxyethynylcarbinols for the preparation of α,β-unsaturated esters by rearranging these compounds with acids.

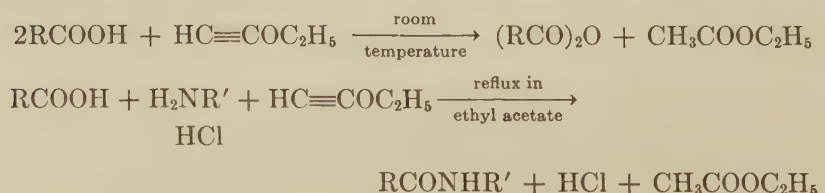


The same application was found independently by Heilbron, Jones, Julia, and Weedon in 1948 (14,15).

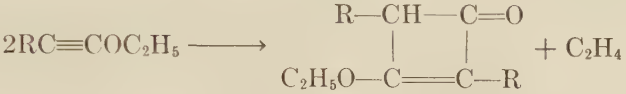
Recently (1959) we discovered that α,β-unsaturated esters can be prepared directly and with good yields by interaction of ethynyl ethers with carbonyl compounds under the influence of boron fluoride (180).

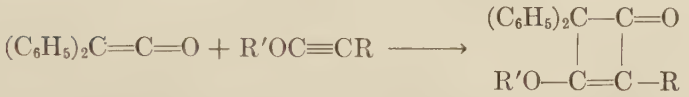


Other attractive and well-developed synthetic methods making use of ethynyl ethers are those for the preparation of acid anhydrides under very mild conditions, dating from 1950 (16,17), and for the formation of amide or peptide bonds, discovered in 1955 (18,19,163).

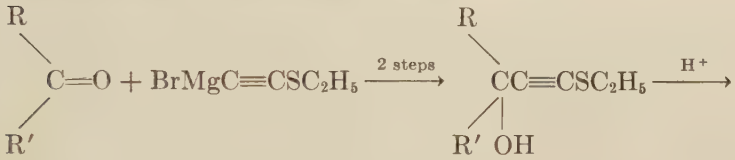


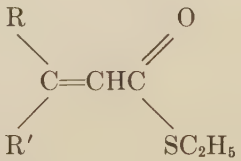
Recently (1957) general methods for the preparation of cyclobutenone ethers from ethoxyalkynes have been found (87,124,173).





The only recorded utilization of an ethynyl thioether is for the preparation of α,β-unsaturated thioesters (20; see also 176,180).





II. Preparations and Properties

A. PREPARATION OF ETHYNYL ETHERS

1. From β-Halogeno α,β-Unsaturated Ethers. Most of the investigators working with ethynyl ethers obtained these compounds by heating β-halogeno α,β-unsaturated ethers with powdered potassium hydroxide (1,3,21–32,160,171).

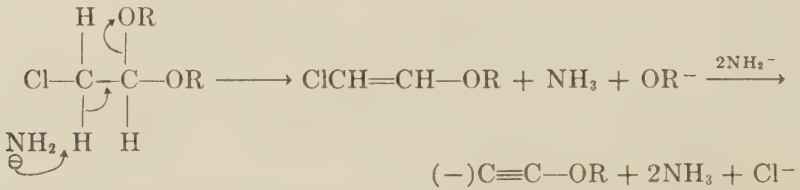
$$RCX{=}CHOR' + KOH \longrightarrow RC{\equiv}COR' + KX + H_2O$$

R = H, alkyl, or aryl; R′ = alkyl or aryl; X = Cl or Br

Yields of 30–90% were obtained.

Other bases, with the exception of sodamide in liquid ammonia (34), are useless. Tertiary alkoxides (e.g., potassium *tert*-butoxide) give a low yield of ethoxyethyne from ethyl β-chlorovinyl ether (37). Other alkoxides liberate chloride ion, but no ethoxyethyne can be isolated, probably because it adds alcohol (see Section III-F-3).

2. From Acetals of Chloroacetaldehyde. Eglinton, Jones, Shaw, and Whiting (17,33) prepared methoxy-, ethoxy-, and butoxyethyne by the interaction of sodamide and chloroacetaldehyde acetals in liquid ammonia. Although at first sight this method seems different from the one just described, it probably also proceeds by way of an alkyl β-chlorovinyl ether.



$$\ominus\text{NH}_2 + \text{H}-\text{C}(\text{H})(\text{OR})-\text{C}(\text{H})(\text{Cl})-\text{OR} \longrightarrow \text{ClCH}{=}\text{CH}{-}\text{OR} + \text{NH}_3 + \text{OR}^- \xrightarrow{2\text{NH}_2^-} (-)\text{C}{\equiv}\text{C}{-}\text{OR} + 2\text{NH}_3 + \text{Cl}^-$$

Treatment of ethyl α,β-dichloro- or α,β-dibromoethyl ether with sodamide in liquid ammonia also yields the sodium derivative of ethoxyethyne, but from a preparative point of view the latter reactions are unsatisfactory (17).

The synthesis of alkynyl ethers of the type R′C≡COR by alkylation of ethers of the type HC≡COR is treated in Section III-B-2.

3. Methods for the Preparation of β-Halogenovinyl Alkyl or Aryl Ethers. The β-halogeno α,β-unsaturated ethers necessary for the synthesis of ethynyl ethers have been obtained in a variety of ways. For the sake of brevity, these methods are indicated by formula schemes only. The symbol R is used when a method has been utilized for more than one substance; otherwise, the actual compound is mentioned.

(*a*) *Type CHX=CHOR ethers:*

$$\text{CH}_2\text{BrCH(OR)}_2 \xrightarrow{\text{Br}_2} \text{CHBr}_2\text{CH(OR)}_2 \xrightarrow[\text{reflux}]{\text{Zn, alcohol}} \text{CHBr}{=}\text{CHOR}$$

Yields are 35–78% based on dibromoacetal (3,15,160).

$$\text{CH}_3\text{CH}_2\text{OH} \xrightarrow[25\text{–}40^\circ]{\text{Cl}_2} \text{CHCl}_2\text{CH(OC}_2\text{H}_5)_2 \xrightarrow[\text{reflux}]{\text{Zn, NH}_4\text{Cl in H}_2\text{O}} \text{CHCl}{=}\text{CHOC}_2\text{H}_5$$

Yield is 72% based on dichloroacetal (28).

$$\text{CH}_3\text{CHO} + \text{ROH} + \text{HCl} \longrightarrow \text{CH}_3\text{CHCl(OR)} \xrightarrow{\text{X}_2} \text{CH}_2\text{XCHX(OR)} \xrightarrow[110\text{–}115^\circ]{\text{diethylaniline}} \text{CHX}{=}\text{CHOR}$$

X = Cl or Br

Yields are moderate to fair (30,36,38).

$$HC{\equiv}CH + ROH \xrightarrow{KOH} CH_2{=}CHOR \xrightarrow{Br_2}$$
$$CH_2BrCHBr(OR) \xrightarrow[100°]{C_6H_5N(C_2H_5)_2} CHBr{=}CHOR$$

Yields are moderate to fair (22,23,27,171).

$$CHBr{=}CHBr + C_6H_5ONa \xrightarrow{\text{in alcohol}} CHBr{=}CHOC_6H_5$$

Yield is 35–45%(1,21).

$$CH_2ClCH(OR)_2 \xrightarrow[150\text{–}200°]{K_2S_2O_7} CHCl{=}CHOR + ROH$$

Yields are 70% (158; see also 162).

(*b*) *Type R'CX=CHOR ethers:*

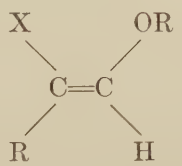
$$R'CH_2CHO + ROH + HCl \longrightarrow R'CH_2CHCl(OR) \xrightarrow{X_2}$$
$$R'CHXCHX(OR) \xrightarrow[\text{or pyridine}]{\text{diethylaniline}} R'CX{=}CHOR$$
$$X = Cl \text{ or } Br$$

Yields are moderate to fair (25,29,29a,30,175).

$$C_6H_5C{\equiv}CH + ROH \xrightarrow{NaOR} C_6H_5CH{=}CHOR \xrightarrow{Br_2}$$
$$C_6H_5CHBrCHBr(OR) \xrightarrow{KOtBu} C_6H_5CBr{=}CHOR$$

Yields are fair (35).

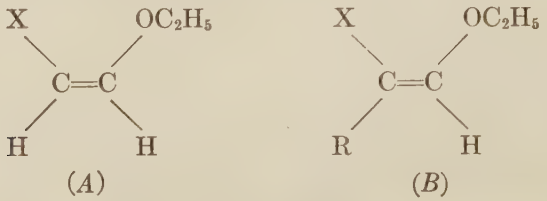
The β-halogeno α,β-unsaturated ethers obtained are mixtures of *cis* and *trans* isomers, the predominating isomers being



Although most investigators did not isolate the pure isomers, these can be obtained by careful fractional distillation (28,29,30,171). Elevated temperatures must be avoided, as they cause interconversion, the product of the distillation being mainly the lower boiling isomer (37). This is invariably the one with the α-hydrogen and β-halogen atoms *cis* to one another.

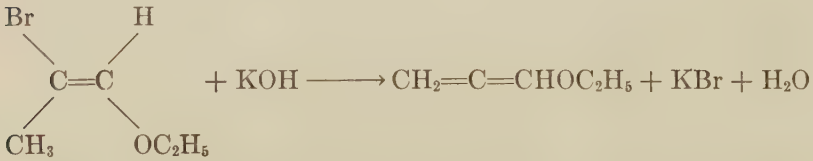
It is very fortunate that the original mixtures are rich in the product with *trans* α-hydrogen and β-halogen, because this configuration —in accordance with the rule of *trans* elimination during dehydrohalogenations with bases—favors the formation of ethynyl ethers. The other isomer reacts sluggishly and can be recovered from the reaction residues (29,37,171).

In the ensuing discussion the terms *cis* and *trans* will be employed in accordance with the conventional usage. In the case of β-halogenovinyl ethers this means that isomer *A*



is termed *cis;* however, the corresponding β-halogenoalkenyl ether, *B* will be named *trans.* Where confusion might arise, the relative positions of α-hydrogen and β-halogen atoms will be indicated.

A *cis*-rich mixture of β-bromopropenyl ethyl ether, on prolonged heating with potassium hydroxide under distillation conditions, has been reported to yield ethoxypropyne contaminated with much ethyl allenyl ether (30; see also 175).



The presence of allenyl ethers can be readily detected by infrared absorption spectrophotometry because these compounds show a strong absorption band at about 5.07 μ (1950 cm.$^{-1}$). Furthermore, the allenyl ethers have a much higher refractive index and a lower boiling point than the isomeric alkynyl ethers (30,31,37).

A slight isomerization of methoxypropyne into methyl allenyl ether by heating with solid potassium hydroxide has been observed (175). According to Hatch and Weiss (31), however, phenoxypropyne cannot be isomerized into phenoxypropadiene.

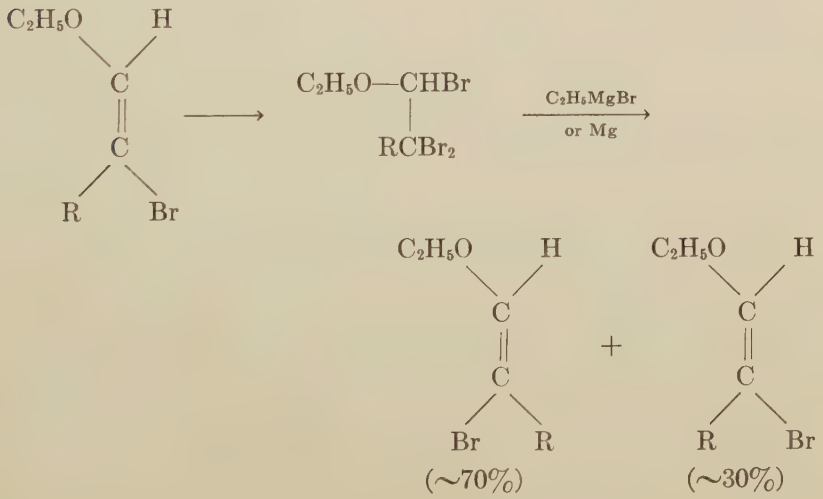
Jacobs (159) has found that allenyl ethers in turn can be converted

into an equilibrium mixture consisting of allenyl and propargyl ether.

$$CH_2{=}C{=}CHOR \overset{\text{alkali}}{\rightleftharpoons} HC{\equiv}CCH_2OR$$

4. Recommended Procedures for the Synthesis of Ethoxyethyne ($HC{\equiv}COC_2H_5$). The easiest method for the preparation of ethoxyethyne, the preferred compound for synthetic applications, appears to be the conversion of chloroacetal with sodamide (33). The dehydrohalogenation with potassium hydroxide of the *cis*-rich mixture of *cis*- and *trans*-ethyl β-chlorovinyl ether obtained by elimination of alcohol from chloroacetal (158,162) is also convenient, however. Chloroacetal is commercially available or can readily be prepared by chlorination of a mixture of paraldehyde and alcohol. Detailed instructions can be found in ref. 162 (cf. also 158).

trans-Ethyl β-chlorovinyl ether eventually recovered from the reaction of the *cis* and *trans* mixture with potassium hydroxide can be partially isomerized into the *cis* compound by irradiation in the presence of small amounts of bromine (162). Ficini (29) effected a partial conversion of *cis*-$RCBr{=}CHOC_2H_5$ into the *trans* isomer by addition of bromine to the double bond and subsequent debromination through the action of ethylmagnesium bromide or metallic magnesium in ether.



The *trans*-ethyl β-chlorovinyl ether can also be used as such for dehydrohalogenation with sodamide in liquid ammonia (34). The steric requirements for this dehydrohalogenation are much less stringent than for the potassium hydroxide procedure (cf. also the dehydrohalogenation of *trans*-1,2-dichloroethene, Section II-C-3).

B. PROPERTIES OF ETHYNYL ETHERS

The known ethynyl ethers are listed in Tables I and II; derivatives still possessing the —C≡CO— group are also included with the exception of alkoxyethynylcarbinols of the type RR′C(OH)C≡COR″, to which a separate table is devoted (Table III).

The ethynyl ethers, HC≡COR, and the 1-alkoxy-1-alkynes, RC≡COR′, are mobile colorless liquids. The lower members have objectionable, musty odors; the higher representatives smell sweeter. Ethoxyethyne is toxic; inhalation of its vapors causes headaches and may be harmful. Jacobs, Cramer, and Hanson (3) report that mice are killed even on short exposure to low concentrations. Ethoxyethynylcarbinols, especially those derived from aldehydes, are irritating to the skin and sometimes cause eczemas (37). *It is therefore advisable to perform all operations with ethynyl ethers in a well-ventilated room, and preferably in a fume-cupboard. Safety glasses should also be worn* (see below).

Phenoxyethyne is rather unstable and polymerizes at room temperature to a deep red liquid and then to a hard, brittle, black, shiny solid (40). This polymerization is discussed in greater detail in Section III-G-6.

The *alkoxy*ethynes, HC≡COR, are more stable and, when pure and sealed in tubes, can be stored at 0° for some time. On exposure to air, a yellow and finally a brown color develops, but by distillation most of the material can be recovered unchanged. Ethereal solutions kept at 0° remain colorless for several days. Ethoxyethyne immediately polymerizes to a red oil when dissolved in liquid sulfur dioxide (37).

Alkoxy- and phenoxyalkynes of the type RC≡COR′ are stable at ordinary temperatures.

By heating ethynyl ethers in sealed tubes above 100°, explosive decomposition with carbonization may occur (3). The author has never observed explosions of ethoxyethyne under normal conditions. This substance has always been prepared and distilled at ordinary pressure in the author's laboratory, and many kilograms of the material in batches up to 100 g. have been handled. Vigorous decompositions—occasionally even violent explosions—of ethoxyethynyl*carbinols*, however, have sometimes been observed by ourselves and by others. These were always caused by careless handling, especially by heating at too high temperatures (cf. Section III-H-1).

TABLE I
Ethynyl Ethers HC≡COR[a]

Compound	Boiling point, °C.	n_D^{20}	Density	Other characteristics	Refs.
$HC{\equiv}COCH_3$	22.5–23.5	n_D^{16} 1.3693	d_4^{20} 0.805		17,*22*,30,*33*,160
$HC{\equiv}COC_2H_5$	51	1.3812	d_4^{20} 0.799	Dipole moment, μ = 1.94 D.	3,17,22,23,24,26,27,28, 33,*39*,171,*193*
$HC{\equiv}CO{\cdot}n\text{-}C_3H_7$	75	1.3935	d_4^{20} 0.8080		*24*
$HC{\equiv}CO{\cdot}iso\text{-}C_3H_7$	69–71	1.3930	—		*187*
$HC{\equiv}CO{\cdot}n\text{-}C_4H_9$	50.5/110 mm.	1.4033	d_4^{25} 0.8078	Dipole moment, μ = 2.03 D.	3,17,24,26,*39*
$HC{\equiv}COC_6H_5$	61.5–61.8/25 mm.	1.5171	d_4^{20} 1.0114	Dipole moment, μ = 1.41 D. (39) m.p. −37 to −36 (*21*)	1,21,31,*40*

[a] From the available data the best values for the physical constants have been selected. The references relating to these values are given in italics.

TABLE II
Ethers RC≡COR'[a]

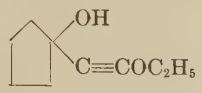
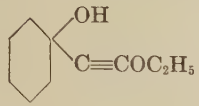
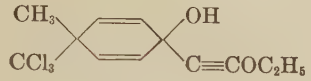
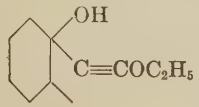
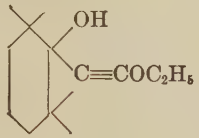
Compound	Boiling point, °C.	n_D^{20}	d_4^{20}	Remarks	Refs.
$CH_3C{\equiv}COCH_3$	65.7–66.3/760 mm.	1.4023	0.836		*175*
$CH_3C{\equiv}COC_2H_5$	88–90.5/760 mm.	1.4108	0.833	Dipole moment, μ = 1.69 D.	25,30,*193*
$CH_3C{\equiv}CO\cdot$iso-C_3H_7	58–59/130 mm.	1.4147	0.823		*175*
$CH_3C{\equiv}CO\cdot n$-C_4H_9	55.2–55.4/33 mm.	1.4239	0.834		*175*
$CH_3C{\equiv}CO\cdot sec$-C_4H_9	58–60/54 mm.	1.4240	—		*187*
$CH_3C{\equiv}CO\cdot$iso-C_4H_9	62–64/70 mm.	1.4214	—		*187*
$CH_3C{\equiv}CO\cdot n$-C_5H_{11}	83–85/52 mm.	1.4314	—		*187*
$CH_3C{\equiv}CO(CH_2)_2CH(CH_3)_2$	81–83/55 mm.	1.4282	—		*187*
$C_2H_5C{\equiv}COCH_3$	88–89/760 mm.	1.4098	0.825		*175*
$C_2H_5C{\equiv}COC_2H_5$	112.5–113/750 mm.	$n_D^{22.5}$ 1.4140	$d_{22.5}^{22.5}$ 0.8234		25,*29*
n-$C_3H_7C{\equiv}COCH_3$	62.5–63.5/129 mm.	1.4175	0.828		*175*
$(CH_3)_2CHC{\equiv}COCH_3$	55.8–56.0/147 mm.	1.4103	0.811		*175*
$(CH_3)_2CHC{\equiv}COC_2H_5$	53–55/60 mm.	1.4140	—		*187*
n-$C_4H_9C{\equiv}COCH_3$	77–78/96 mm.	1.4244	0.831		*175*
n-$C_4H_9C{\equiv}COC_2H_5$	—	—	—		17
n-$C_5H_{11}C{\equiv}COCH_3$	49–50/10 mm.	1.4290	0.833		*175*
n-$C_5H_{11}C{\equiv}COC_2H_5$	69–70/14 mm.	n_D^{24} 1.4295	d_{24}^{24} 0.8302		*29*
n-$C_6H_{13}C{\equiv}COCH_3$	67.3–67.5/10.5 mm.	1.4332	0.833		*175*

n-$C_8H_{17}C{\equiv}COCH_3$	77–78/1.75 mm.	1.4393	0.834		*175*
$CH_3C{\equiv}COC_6H_5$	52.5–53/2 mm.	1.5295	1.0251		*31*
$C_2H_5C{\equiv}COC_6H_5$	98–99/20 mm.	1.5179	0.9823		*21*
n-$C_4H_9C{\equiv}COC_6H_5$	122–123/14 mm.	1.5090	0.9551		*21*
$C_6H_5C{\equiv}COCH_3$	55–58/1 mm.	1.5481	d_4^{25} 1.0149	Dimer, m.p. 134–135°	*32*
				Trimer, m.p. 165–166°	
$C_6H_5C{\equiv}COC_2H_5$	49–50/0.5 mm. (impure sample)	—	—	Trimer, m.p. 170–170.5°	*32*
$CH_2CHCH_2C{\equiv}COC_2H_5$ (O)	63–64/3 mm.	1.4508	—	From epichlorohydrin and $LiC{\equiv}COC_2H_5$ in NH_3	*178*
$C_2H_5OOCC{\equiv}COC_2H_5$	62–64/2 mm.	1.4480	—	Very unstable, impure sample (from ethyl chloroformate and $LiC{\equiv}COC_2H_5$)	*37*
$BrC{\equiv}COC_6H_5$	—	—	—	Very unstable, lachrimatory, explosive	41
$IC{\equiv}COC_2H_5$	32–33.5/2 mm.	1.5268	—	Very unstable, forms ethyl iodoacetate with H_2O + HCl	*37*
$CH_3OC{\equiv}C(CH_2)_3C{\equiv}COCH_3$	55–59/0.15 mm.	1.4682	0.966		*177*
$C_2H_5OC{\equiv}C(CH_2)_3C{\equiv}COC_2H_5$	82–85/0.2 mm.	1.4662	0.934		*177*
$CH_3OC{\equiv}C(CH_2)_4C{\equiv}COCH_3$	62/0.12 mm.	1.4660	—		*177*

[a] From the available data the best physical constants have been selected. The references relating to these values are given in italics.

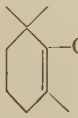
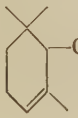
TABLE III
Alkoxyethynylcarbinols and Related Compounds[a]

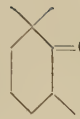
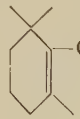
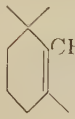
Compound	Boiling point, °C.	n_D^{20}	Remarks	Refs.
$CH_3CH(OH)C{\equiv}COC_2H_5$	79.5–81/13 mm.	1.4470		*85*,171
$CH_3CH(OH)C{\equiv}COC_6H_5$	88–89/1 mm.	1.5351	d_4^{20} 1.0846	*21*
$CH_3CH_2CH(OH)C{\equiv}COC_2H_5$	68–71/3 mm.	1.4514		*85*
$(CH_3)_2C(OH)C{\equiv}COC_2H_5$	72/11 mm.	1.4420	d_4^{20} 0.9391 (*13*)	13,*15*, 143, 171
$CH_3(C_2H_5)C(OH)C{\equiv}COC_2H_5$	73–74/8 mm.	1.4470	d_4^{20} 0.9357	*171*
$(CH_3)_2C(OH)C{\equiv}COC_6H_5$	91–92/1 mm.	1.5220	d_4^{20} 1.0470	*21*
$(CH_3)_3CCH(OH)C{\equiv}COC_2H_5$	100/18 mm.	—		*161*
$CH_3(CH_2)_5CH(OH)C{\equiv}COC_2H_5$	80/10^{-3} mm.	1.4566		*85*
$(CH_3)_3CCOC(OH)[C(CH_3)_3]C{\equiv}COC_2H_5$	—	—	b	169
$(CH_3O)_2CHCH_2C(CH_3)(OH)C{\equiv}COC_2H_5$	88/0.6 mm.	—		*114*
$CH_3CH{=}CHCH(OH)C{\equiv}COC_2H_5$ (*trans*)	66.5/0.3 mm.	1.4733		*37*
$C_2H_5SCH_2CH{=}CHCH(OH)C{\equiv}COC_2H_5$	50–55/10^{-3} mm.	1.5156		*37*
$CH_2{=}C(CH_3)C(CH_3)(OH)C{\equiv}COC_2H_5$	66–67/3 mm.	1.4640	d_4^{20} 0.9468	*171*
$CH_2{=}CHC(CH_3)(OH)C{\equiv}COC_2H_5$	54–55/0.1 mm.	1.4590		*15*
$(CH_3)_2C{=}CHC(CH_3)(OH)C{\equiv}COC_2H_5$	64–65/2 mm.	1.4736	d_4^{20} 0.9590	*171*
$CH_2{=}C(CH_3)(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	82–84/1 mm.	n_D^{23} 1.4635	d_{23}^{23} 0.9258	92,*105*
$(CH_3)_2C{=}CHCH{=}CHC(CH_3)(OH)C{\equiv}COC_2H_5$	83–93/0.04–0.2 mm.	1.5460	d_4^{20} 0.9699	*171*
$CH_2{=}C(CH_3)(CH_2)_3C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	98
$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	79–80/0.01 mm.	1.4678	d_4^{20} 0.9237	11,*171*
$CH_2{=}CHC(CH_3)_2CH_2C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	93
$CH_3(C_2H_5)C{=}CH(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	94–97/0.02 mm.	1.4684	d_4^{20} 0.9234	*171*
$CH_3(iso\text{-}C_2H_7)C{=}CH(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	101-103/0.1 mm.	1.4680	d_4^{20} 0.9156	*171*

$(iso\text{-}C_3H_7)_2C{=}CH(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	118–120/1 mm.	1.4653	d_4^{20} 0.9024	*171*
$CH_3(tert\text{-}C_4H_9)C{=}CH(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	116–118/1 mm.	1.4705	d_4^{20} 0.9147	*171*
$CH_3(Cl)C{=}CH(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	105–107/0.5 mm.	1.4817	d_4^{20} 1.0430	*171*
$(CH_3)_2C{=}C(CH_3)(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	80–82/0.1 mm.	1.4730	d_4^{20} 0.9258	*27*,107
$(CH_3)_2CHC(=CH_2)(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	108
$CH_2{=}C(CH_3)(CH_2)_2C(CH_3){=}CH(CH_2)_3C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	92
$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH(CH_2)_2C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	94
$CH_3[C(CH_3){=}CHCH_2CH_2]_3C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	96
	91/3 mm.	1.4786		*143*
	102–103/3 mm. m.p. 7.5–8.0	1.4839		*143*,115, 171
	—	—	b,c	168
	110–111/4 mm.	—		34,*110*
	103.5–104/2 mm.	—		*167*

(*continued*)

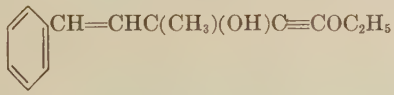
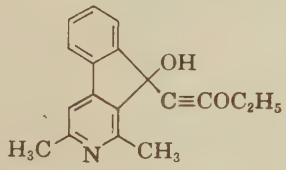
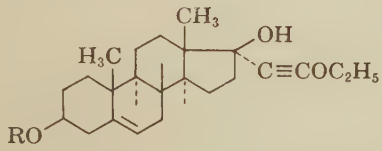
TABLE III (*continued*)

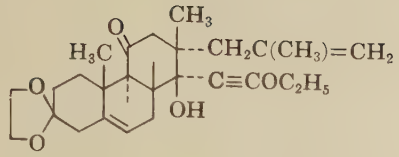
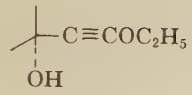
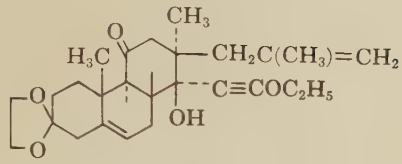
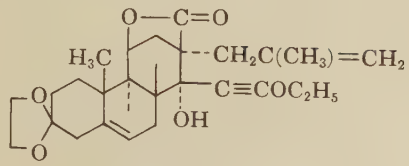
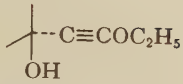
Compound	Boiling point, °C.	n_D^{20}	Remarks	Refs.
OH $C{\equiv}COC_2H_5$	78–81/0.1 mm.	n_D^{25} 1.489		*34*
$CH{=}CHC(CH_3)(OH)C{\equiv}COC_2H_5$ (Δ^2 *trans*) Δ^2	80–100/10^{-6} mm.	n_D^{15} 1.5143		11,*15*, 88
$CH_2CH_2C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	9
 $CH_2CH_2C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	90
 $CH_2CH_2C(CH_3)(OH)C{\equiv}COC_2H_5$	—	—	b	90

	—	—	b	34
	—	—	b	34
	—	—	b	34
	—	—	b	15
 Δ^2 Δ^3 Δ^4	—	—	b	12,103
(all *trans*)				
Δ^2,Δ^4 *trans*, Δ^3 *cis*	—	—	b	104
	70–75/10^{-3} mm.	1.5422		*85*
	98–100/0.1 mm.	—		*11*,13

(continued)

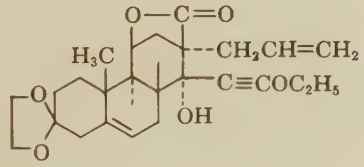
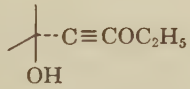
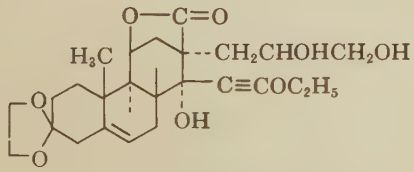
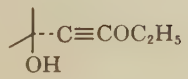
TABLE III (*continued*)

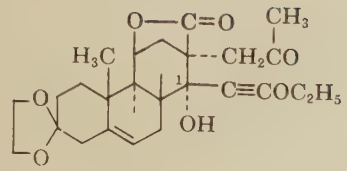
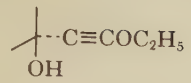
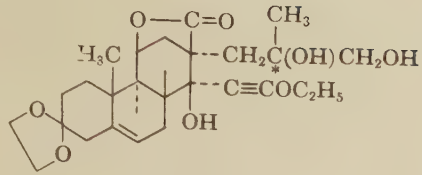
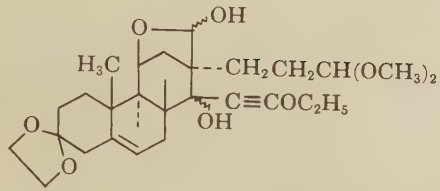
Compound		Boiling point, °C.	n_D^{20}	Remarks	Refs.
		—	—	b	13,15
		m.p. 125–126	—		*95*
	R = H	m.p. 140–141	—	$[\alpha]_D^{19}$ −124° (c = 0.985 in $CHCl_3$)	*89*
	R = CH_3CO	m.p. 139–140	—	$[\alpha]_D^{19}$ −122° c = 0.942 in $CHCl_3$	*89*

	m.p. 114–115.5 and 131–132	—	100a, *100b*
	m.p. 159–161	—	100a, *100b*
	m.p. 133–134	—	100a, *100b*
	m.p. 173–174d.		*101*
	m.p. 147–148d.	—	*101*

(*continued*)

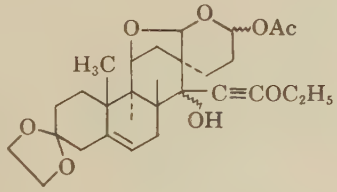
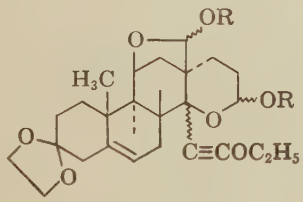
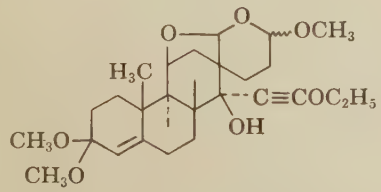
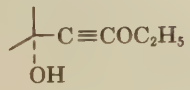
TABLE III (*continued*)

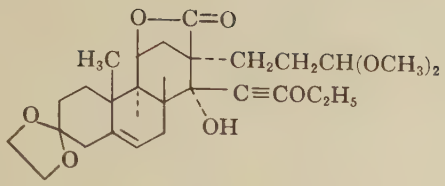
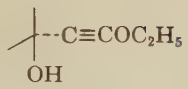
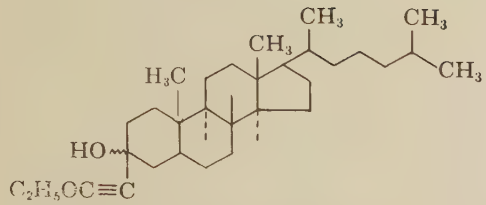
Compound	Boiling point, °C.	n_D^{20}	Remarks	Refs.
	m.p. 180–182	—		*112*
	m.p. 149–152	—	Partial reduction of C≡C bond occurs together with reduction of allyl group	*112*
	m.p. 222.5–224	—		*112*
	m.p. 149–152	—		*112*

	m.p. 183–184d.	—		*101*
	m.p. 157–158d.	—		*101*
	m.p. 127–153.5d.	—	Mixture of isomers at C*	*101*
	m.p. 157	—		*165*

(continued)

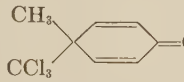
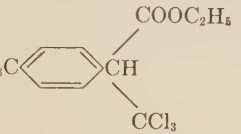
TABLE III (*continued*)

Compound	Boiling point, °C.	n_D^{20}	Remarks	Refs.
	m.p. 166–168	—		*165*
 R = H {stereo-isomers	m.p. 179–181 m.p. 154–156	— —		*165*
R = Ac {stereo-isomers	m.p. 182 184 m.p. 158–160	— —		*165*
	m.p. 179–180	—		*165*
	m.p. 194–195	—		*165*

	m.p. 156 157	—	*165*
	m.p. 143–144	—	*165*
	m.p. 85–86 (from acetone)[d]	—	*170*

[a] From the available data the best values for the physical constants have been selected. The references relating to these values are given in italics

[b] The substance has not been prepared in analytically pure condition but was used directly for further transformations.

[c] This carbinol on standing rearranges first to  and then to 

[d] Crystals containing 1 mole of acetone per 2 moles of carbinol. From other solvents no crystals can be obtained.

The dielectric constants of some ethynyl ethers have been measured by Jacobs, Roberts, and MacMillan and from these the dipole moments were calculated (39). The values found are listed in Table I.

Coats and Anderson (148) have determined the appearance potentials of the ions $C_6H_5O(+)$ and $C_6H_5(+)$ for phenoxyethyne by direct electron impact. The values are 9.5 ± 0.1 and 12.2 ± 0.1 v., respectively.

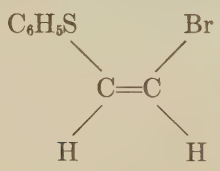
C. PREPARATION OF ETHYNYL THIOETHERS (HC≡CSR) AND THEIR DERIVATIVES (RC≡CSR′)

1. From β-Halogeno α,β-Unsaturated Thioethers. The methods used for the synthesis of ethynyl thioethers are somewhat similar to those already mentioned in connection with the oxygen analogs and comprise the dehydrohalogenation of β-halogenated α,β-unsaturated thioethers by base. Satisfactory yields are obtained (3b,5,6,20,42,43, 182,184).

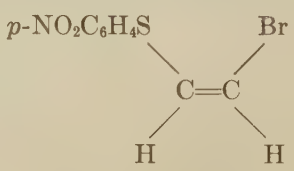
$$RCX{=}CHSR' \xrightarrow{KOH} RC{\equiv}CSR'$$

The ease of these dehydrohalogenations, just as in the case of the oxygen analogs, depends upon the structure. A *trans* relationship of the α-hydrogen and β-halogen atoms again is favorable (3b). Powdered potassium hydroxide is usually employed for the dehydrohalogenation, but alcoholic potassium hydroxide can also be used. Prolonged reaction times and high temperatures must then be avoided, however, as these may cause addition of alcohol to the triple bond (3b,20,42,43,182). The isomers with *cis* α-hydrogen and β-halogen atoms can be dehydrohalogenated readily by sodamide in liquid ammonia (42,43).

As expected, the eliminations are greatly favored by electron-attracting groups on appropriate positions in R′. Thus, Montanari *et al.* (42,43) found that at 25° a five-fold excess of 1*N* alcoholic potassium hydroxide quantitatively eliminates hydrogen bromide from *cis*-1-bromo-2-(phenylthio)ethene (III) in $^1/_2$ hr., whereas the elimination from *cis*-1-bromo-2-(*p*-nitrophenylthio)ethene (IV) is



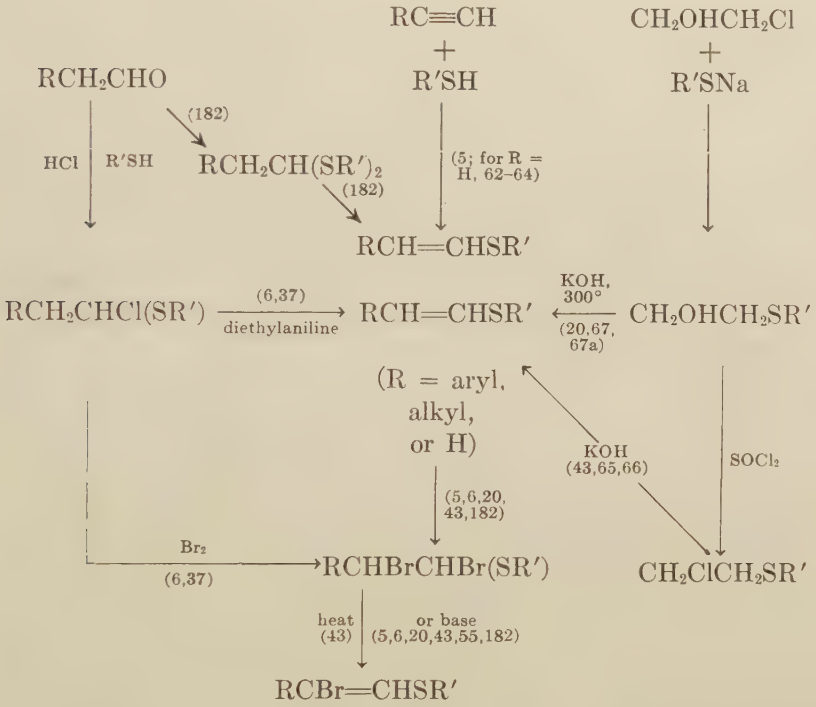
(III)



(IV)

completed in 1 min. The latter compound is so easily dehydrohalogenated that it is even partly converted into the ethynyl thioether during chromatography over aluminum oxide (42,43).

2. Methods for the Preparation of β-Halogeno α,β-Unsaturated Thioethers: (*a*) *Type RCX=CHSR′ thioethers.*



$$R = H, R' = Ar \begin{cases} 70\%\ cis + 30\%\ trans \text{ (by heat) (43)} \\ 50\%\ cis + 50\%\ trans \text{ (by base) (55)} \end{cases}$$

It is interesting to note that the dibromides, RCHBrCHBr(SR′), by treatment with two molecules of alcoholic potassium hydroxide can be converted directly into the ethynyl thioether (5). However, Montanari *et al.* (43) have reported that 1-ethoxy-2-(phenylthio)-ethene rather than phenylthioethyne is obtained from 1,2-dibromoethyl phenyl thioether and slightly more than one mole of potassium hydroxide in ethanol.

(*b*) *Type RSCH=CHX thioethers from ethyne* (42,43,45,46,61; cf. also 47–52).

$$ArSCl + HC{\equiv}CH \xrightarrow[\text{when Ar = 2,4-dinitroC}_6H_3\text{, AlCl}_3\text{ is added (51)}]{\text{ethyl acetate, } -10^\circ} ArSCH{=}CHCl$$

*trans** (α-H, β-Cl *cis*)

(*c*) *Type RSCH=CHX thioethers from ethynecarboxylic acid.*

$$HC{\equiv}CCOOH \xrightarrow{HCl} ClCH{=}CHCOOH \xrightarrow[NaHCO_3]{ArSH}$$

cis (59) or *trans* (60)

$$ArSCH{=}CHCOOH \xrightarrow[CH_3COOH]{\text{halog.}} ArSCHXCHXCOOH \xrightarrow{(H_2O)}$$

cis or *trans* (V)

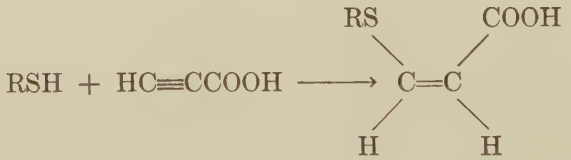
threo from *cis* erythro from *trans* (55)

$$ArSCH{=}CHX + CO_2 + HX$$

80–90% *cis* + 10–20% *trans* (53,55)

Satisfactory yields are reported (3b,53–56,58; cf. also 57).

cis-V can also be obtained by (*trans*) addition of sodium arylthiolate to propiolic acid (54,56).



(*d*) *Type RSCH=CHX thioethers from chloroethyne.* Maioli and Modena (195) have reported that thiophenols can be added to the mercuric derivative of chloroethyne, yielding a *cis* adduct:

* *trans*-β-Chlorovinyl-(*p*-nitrophenyl)thioether (α-H, β-Cl *cis*) has been partly isomerized into the *cis* isomer by irradiation of a solution in benzene with ultraviolet light (3a); separation is effected by chromatography over Al_2O_3.

$$Hg(C{\equiv}CCl)_2 + ArSH \xrightarrow[\text{ethanol–ether}]{\text{morpholine in}} \begin{matrix} ArS & & Cl \\ & \diagdown\ \diagup & \\ & C{=}C & \\ & \diagup\ \diagdown & \\ H & & H \end{matrix}$$

3. From Sulfenyl Halides. A second method for the preparation of ethynyl thioethers comprises a reaction between phenylsulfenyl chloride and the Grignard derivative of phenylethyne in ether (5).

$$C_6H_5SCl + BrMgC{\equiv}CC_6H_5 \longrightarrow C_6H_5SC{\equiv}CC_6H_5$$

4. From Ethenylene 1,2-Bisthioethers. A third and very interesting method has been reported by Parham and Stright (4), who obtained (phenylthio)ethyne by treating 1,2-bis(phenylthio)ethene with butyllithium. (It is interesting to note that Fromm and Siebert (71) observed elimination of *p*-toluenethiol from 1,2-bis(*p*-tolylthio)ethene by sodium ethoxide. Possibly there, too, an (arylthio)ethyne was formed.) The yields are satisfactory. The *cis* as well as the *trans* isomer reacts rapidly.

$$C_6H_5SCH{=}CHSC_6H_5 + 2\ LiBu \xrightarrow[\text{in ether}]{0^\circ} C_6H_5SLi + 2BuH + LiC{\equiv}CSC_6H_5$$

Before hydrolysis of the reaction mixture the thiolate must be removed, either by filtration or by reaction with one mole of an alkyl halide, because otherwise recombination occurs easily (44,140,176) and the only product obtained is the starting material.

This method is also applicable to the preparation of (ethylthio)-ethyne from 1,2-bis(ethylthio)ethene or even from 1-ethoxy-2-(ethylthio)ethene (obtained from ethoxyethyne and ethanethiol; see Section III-F-1) (44,200).

$$C_2H_5OCH{=}CHSC_2H_5 + 2LiBu \longrightarrow C_2H_5OLi + LiC{\equiv}CSC_2H_5 + 2BuH$$

Instead of butyllithium, sodamide in liquid ammonia can be used for the conversion of 1,2-bis(ethylthio)ethene (176).

Because these methods initially produce the lithium or sodium derivative of ethynyl thioethers, they can also be used for the preparation of alkynyl thioethers by subsequent reaction with an excess of an alkylating agent. Satisfactory yields are obtained (176).

$$NaC{\equiv}CSR + R'X \longrightarrow R'C{\equiv}CSR + NaX$$

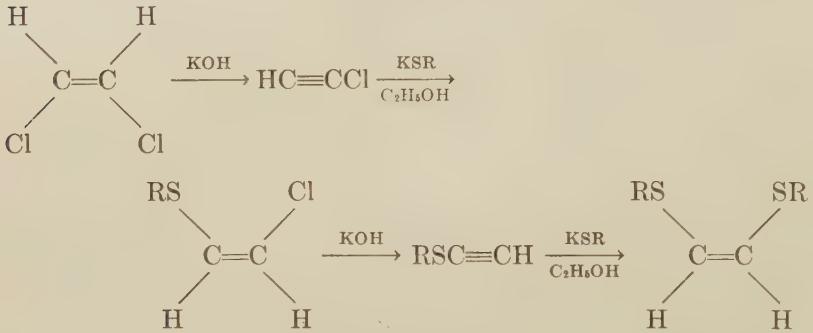
Similarly, addition of a carbonyl compound produces (alkyl(or aryl)-thio)ethynylcarbinols (cf. Section III-C-2).

The required 1,2-bis(aryl(or alkyl)thio)ethenes can be obtained (7,71) by refluxing *cis*-1,2-dichloroethene with an alcoholic solution of a thiol and excess potassium hydroxide (see also 8,70–78) or by treating *cis*-1,2-dichloroethene with sodium thiolate in liquid ammonia (176).

$$\underset{cis}{ClCH{=}CHCl} + 2KSR \xrightarrow[C_2H_5OH]{KOH} \underset{cis}{RSCH{=}CHSR} + 2KCl$$

Excellent yields are obtained, especially with thiophenols (71).

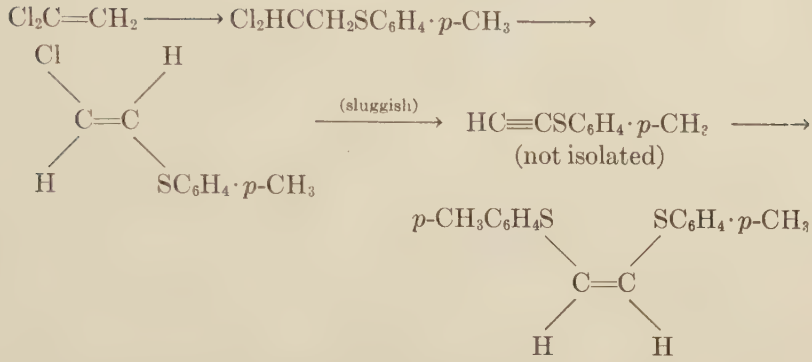
Truce *et al.* (73) have proved that only *cis*-1,2-dichloroethene reacts. The process proceeds by way of eliminations and additions; the end product has the *cis* configuration.



The easiest route to *cis*-1,2-bis(aryl(or alkyl)thio)ethenes consists of treating the cheap commercial mixture of *cis*- and *trans*-1,2-dichloroethene in liquid ammonia with sodamide. This base is sufficiently reactive to convert both isomers into the sodium derivative of chloroethyne (189); addition of thiol to this mixture then produces the desired compound (176).

The *cis* isomers of 1,2-bis(arylthio)ethenes are converted partly to the *trans* isomers by heating (74,75,77,79).

Truce and Boudakian have reported that *cis*-bis(*p*-tolylthio)ethene (R = *p*-$CH_3C_6H_4$) can also be obtained from vinylidene chloride and sodium *p*-toluenethiolate. This process probably takes the following course (61):



D. PROPERTIES OF ETHYNYL THIOETHERS

Almost all ethynyl thioethers, HC≡CSR, are colorless liquids with peculiar odors. The smell of (ethylthio)ethyne is similar to that of ethoxyethyne.

The stability of most of the aromatic compounds seems to be poor. They rapidly turn brown, even in sealed tubes at 0° (43), although (*p*-nitrophenylthio)ethyne is a rather stable solid (m.p. 74°).

Aliphatic ethynyl thioethers appear to be considerably more stable. Ethylthioethyne remains unaltered if kept for a few days at 0°, and the higher (ethylthio)alkynes, $RC{\equiv}CSC_2H_5$, are stable at room temperature in sealed tubes (182).

The aromatic compounds possessing an ethynylic hydrogen atom have been characterized as beautifully crystalline mercuric salts, $Hg(C{\equiv}CSAr)_2$ (4,5,43); the silver salts are also crystalline (43). These metal derivatives soon decompose when stored.

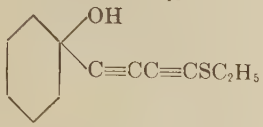
The ethynyl thioethers seem to be nonexplosive. In Table IV all known compounds and their derivatives still possessing the C≡CSR group are listed. The preparation of these derivatives will be discussed in Section III-B-2. A separate table (Table V) is devoted to (alkylthio)ethynylcarbinols. Table IV also contains the data on (phenylseleno)ethyne, which has been prepared by Chierici and Montanari (68). This is the only known selenoethynyl compound of the type HC≡CSeR.

E. PREPARATION AND PROPERTIES OF ETHYNYLENE BISTHIOETHERS (RSC≡CSR)

These substances can be obtained from ethenylene bisthioethers by addition of halogen (Cl_2 or Br_2) and subsequent elimination of two

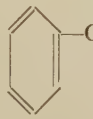
TABLE IV
Thioethers HC≡CSR and R'C≡CSR[a]

Compound	Boiling point, °C.	n_D^{20}	d_4^{20}	Further characteristics	Ref.
$HC{\equiv}CSCH_3$	70.5–71/760 mm.	1.4855	—		*20*
$HC{\equiv}CSC_2H_5$	91.5–92/760 mm.	1.4790	0.915	Dipole moment, μ = 1.64 D	*6,44,193*
$HC{\equiv}CSCH(CH_3)_2$	100/760 mm.	1.4714	—		*184*
$HC{\equiv}CS{\cdot}n\text{-}C_4H_9$	83/93 mm.	n_D^{25} 1.4690	—		*200*
$HC{\equiv}CSC(CH_3)_3$	51.2–52.5/72 mm.	1.4667	—	m.p. −24 to −21.5° Sulfone, m.p. 113–115° (*37*)	*6*
$HC{\equiv}CSC_6H_5$	78–79/7 mm.	n_D^{25} 1.5938	—	Hg^{2+} salt, m.p. 137–138.5° Ag^+ salt, m.p. 141–143°	3b,4,42,43
$HC{\equiv}CSC_6H_4{\cdot}p\text{-}CH_3$	77–79/3 mm.	1.5721	—	Hg^{2+} salt, m.p. 145.5–146.5° Ag^+ salt, m.p. 165–166°	5,42,*43*
$HC{\equiv}CSC_6H_4{\cdot}o\text{-}CH_3$	76–77/3 mm.	—	—	Hg^{2+}, salt, m.p. 137–139° Ag^+ salt, m.p. 167°	42,*43*
$HC{\equiv}CSC_6H_4{\cdot}p\text{-}OCH_3$	101–102/4 mm.	—	—	Hg^{2+} salt, m.p. 202–204°	*43*
$HC{\equiv}CSC_6H_4{\cdot}p\text{-}Cl$	75–76/3 mm.	—	—	Hg^{2+} salt, m.p. 159–161°	*43*
$HC{\equiv}CSC_6H_4{\cdot}o\text{-}Cl$	85–86/3 mm.	—	—	Hg^{2+} salt, m.p. 207°	*43*
$HC{\equiv}CSC_6H_4{\cdot}p\text{-}NO_2$	m.p. 74–75	—	—	Hg^{2+} salt, m.p. 232–234° Ag^+ salt, m.p. 168° (expl.)	42,*43*
$CH_3C{\equiv}CSCH_3$	114–116/760 mm.	1.5030	—		*182*
$CH_3C{\equiv}CSC_2H_5$	136/760 mm.	1.4950	0.924	Dipole moment, μ = 1.63 D (*193*)	*182*
$CH_3C{\equiv}CS{\cdot}n\text{-}C_4H_9$	65–67/12 mm.	1.4860	—		*37*
$CH_3C{\equiv}CS{\cdot}tert\text{-}C_4H_9$	59/26 mm.	1.4826	—		*176*
$CH_3C{\equiv}CSC_6H_5$	78–81/0.75 mm.	n_D^{25} 1.5953	—	Sulfone, m.p. 68.5–69.5°	*4*
$C_2H_5C{\equiv}CSCH_3$	80/122 mm.	1.4960	—		*184*
$C_2H_5C{\equiv}CSC_2H_5$	52/17 mm.	1.4890	—		*176*

n-$C_4H_9C{\equiv}CS{\cdot}n$-$C_4H_9$	120/20 mm.	1.4812	—		*176*
n-$C_5H_{11}C{\equiv}CSCH_3$	79/11 mm.	1.4881	—		*184*
n-$C_5H_{11}C{\equiv}CSC_2H_5$	70–71/2.5 mm.	1.4845	d_{15}^{15} 0.885		*182*
$C_6H_5C{\equiv}CSC_6H_5$	155–158.5/2 mm.	n_D^{25} 1.6593–1.6652	—	Sulfone, m.p. 73–74°	*5*
$HOOCC{\equiv}CSC_2H_5$	58–65/10^{-3} mm.	—	—	*S*-Benzylthiuronium salt, m.p. 165.5–166.5°	*20*
$C_2H_5OOCC{\equiv}CSC_2H_5$	80–82/1 mm.	1.5098	—		*20*
n-$C_3H_7OOCC{\equiv}CSC_2H_5$	95–97/0.5 mm.	1.5028	—		*198*
n-$C_4H_9OOCC{\equiv}CSC_2H_5$	91–93/0.1 mm.	1.4980	—		*198*
$C_6H_5NHCOC{\equiv}CSC_2H_5$	m.p. 75–75.5	—	—		*69*
$CH_3COC{\equiv}CSC_2H_5$	55/0.4 mm.	1.5335	—	From Ac_2O and $LiC{\equiv}CSC_2H_5$ at −20°C. 2,4-Dinitrophenylhydrazone, m.p. 115–116°	*198*
$(C_2H_5SC{\equiv}C)_2$	92–94/0.3 mm.	1.6526	—	Yellow oil	*20*
$[(CH_3)_3CSC{\equiv}C]_2$	m.p. 49.5–51	—	—	Pale yellow crystals	*20*
	m.p. 52–53	—	—		*37*
$CH_2OHCH{=}CHC{\equiv}CSC_2H_5$	98–99/2 mm.	1.5718			*178*
Added for the sake of completeness:					
$HC{\equiv}CSeC_6H_5$	104–105/17 mm.	—	–	Ag^+ salt, m.p. 123°	*68*

[a] From the available data the best values for the physical constants have been selected. The references relating to these values are given in italics.

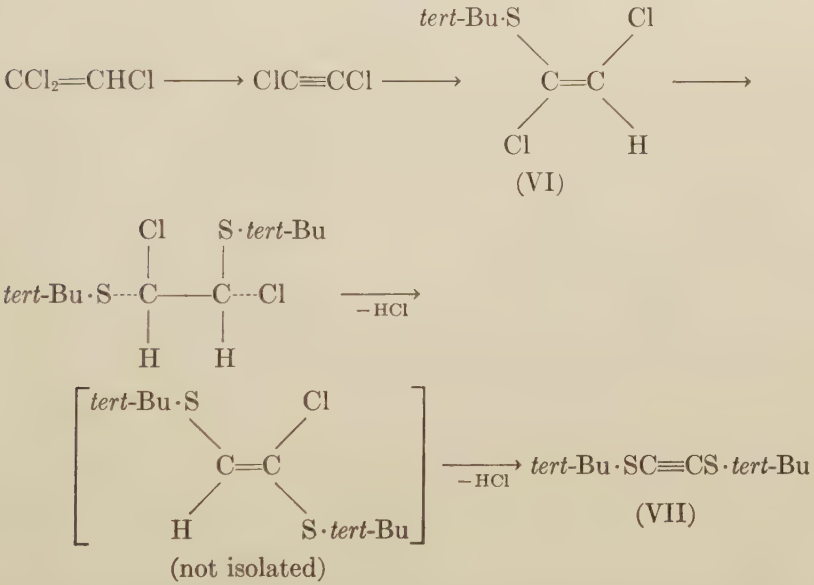
TABLE V
(Alkylthio)ethynylcarbinols[a]

Compound	Boiling point, °C.	Melting point, °C.	n_D^{20}	Ref.
$CH_3CH(OH)C{\equiv}CSC_2H_5$	93.5–95.5/8.5 mm.	—	1.5147	*20*
$(CH_3)_2C(OH)C{\equiv}CSCH_3$	92–92.5/17 mm.	1–2	1.5089	*20*
$(CH_3)_2C(OH)C{\equiv}CSC_2H_5$	89.7–90.7/10 mm.	—	1.5016	*20*,44
$(CH_3)_2C(OAc)C{\equiv}CSC_2H_5$	97–100/15 mm.	—	1.4848	*20*
	109–110.5/2.5 mm.	37.5–38.5	—	*20*,44
	80–101/10^{-4} mm.	—	1.5843	*20*,44
$CH_2{=}CHCH(OH)C{\equiv}CSC_2H_5$	30–40/10^{-3} mm.	—	1.5272	*37*

[a] From the available data the best values for the physical constants have been selected. The references relating to these values are given in italics.

moles of hydrogen halide, either in one operation with boiling alcoholic potassium hydroxide (7,8,71) or in two steps. The first mole may be removed simply by heating (70) and the second by refluxing with alcoholic potassium hydroxide.

Backer and Strating (8) obtained 1,2-bis(*tert*-butylthio)ethyne from trichloroethene and a refluxing solution of sodium *tert*-butylthiolate in alcohol. The reaction product also contained 1-*tert*-butylthio-1,2-dichloroethene (VI) (cf. also 80–82). Possibly the synthesis proceeds as follows:



The known ethynylene bisthioethers are listed in Table VI. Most of these substances are solids.

F. INFRARED CHARACTERISTICS OF ETHYNYL ETHERS AND THIOETHERS

The infrared absorption spectra of the ethynyl ethers and thioethers show some easily recognizable medium to strong bands caused by the ethynylic system. The positions of these absorptions are sum-

TABLE VI
Bisthioethers RSC≡CSR[a]

Compound	Boiling point, °C.	Melting point, °C.	Further characteristics	Ref.
$C_2H_5SC{\equiv}CSC_2H_5$	97/12 mm.	—	n_D^{25} 1.5610 d_4^{25} 1.0510 Dichloride, b.p. 132–134°/12.5 mm. Tetrachloride, m.p. 56°	*70*
$(CH_3)_3CSC{\equiv}CSC(CH_3)_3$	—	40	Disulfone, m.p. 145–146°	*8*
$C_6H_5CH_2SC{\equiv}CSCH_2C_6H_5$	—	53	Yellow crystals Disulfone, m.p., 212°	*7,72*
p-$CH_3C_6H_4SC{\equiv}CSC_6H_4{\cdot}p$-$CH_3$	—	101–102	Dibromide, m.p. 99–100°	*71*
o-$NO_2C_6H_4SC{\equiv}CSC_6H_4{\cdot}o$-$NO_2$	—	225 (expl.)	Yellow crystals Dibromide, m.p. 209°	*7*

[a] From the available data the best values for the physical constants have been selected. The references relating to these values are given in italics.

marized in Table VII (4,5,31,37,168-170,175-178,182,184,187). For many compounds no data have been reported.

TABLE VII
Infrared Absorptions of Ethynyl Ethers and Thioethers

Type of compound	HC≡ stretching vibration	C≡C stretching vibration
HC≡COR (R = alkyl; no values reported for R = aryl)	3.00 ± 0.05 μ (3330 cm.$^{-1}$)	4.65 ± 0.05 μ (2150 cm.$^{-1}$)
R′C≡COR (including carbinols >C(OH)C≡COR)	Absent	4.35–4.50 μ (2220–2300 cm.$^{-1}$)
HC≡CSR (R = alkyl or aryl) and HC≡CSO_2 alkyl	3.05 ± 0.04 μ (3280 cm.$^{-1}$)	4.90 ± 0.05 μ (2040 cm.$^{-1}$)
R′C≡CSR (including carbinols >C(OH)C≡CSR)	Absent	4.4–4.7 μ (2130–2270 cm.$^{-1}$, mostly around 4.6 μ (2170 cm.$^{-1}$)), very weak for RC≡CSR′ (R and R′ = alkyl)
RSC≡CC≡CSR (R = alkyl)	Absent	4.8 μ (2080 cm.$^{-1}$) (strong) and 4.6–4.7 μ (2130–2170 cm.$^{-1}$) (weak)
R′C≡CC≡CSR (R = alkyl)	Absent	4.5–4.6 μ (2170–2230 cm.$^{-1}$) (strong) and 4.8μ (2080 cm.$^{-1}$) (medium)
RSC≡CSR		No values reported

Oxidation of the thioether grouping to a sulfone leaves the position of the C≡C stretching band almost unchanged (4,5,37). The values do not deviate much from those reported for other ethynylic systems, viz., 3.0–3.15 μ (3180–3330 cm.$^{-1}$) for the HC≡ stretching band and 4.4–4.8 μ (2080–2270 cm.$^{-1}$) for the C≡C stretching band (86).

III. Reactions

A. GENERAL OUTLINE OF THE REACTIVITY OF ETHYNYL ETHERS AND THIOETHERS

From a consideration of the structure of the ethynyl *oxygen* ethers,

$$\underset{\beta}{HC}\overset{\curvearrowleft}{\equiv}\underset{\alpha}{C}\overset{\curvearrowright}{-}O\text{–alkyl},$$

we may expect the following types of reactions to take place:

1. Substitution of the ethynylic hydrogen atom (e.g., by metals and by halogen atoms). This is a general property of all compounds possessing such a hydrogen atom.

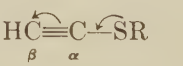
2. Additions to the triple bond. (*a*) Electrophilic reagents will add to the β-carbon atom. (*b*) Nucleophilic reagents will add to the α-carbon atom.

3. Polymerizations and related reactions.

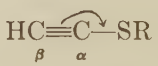
4. Reactions of the ether function.

All four types of conversions as well as some free-radical additions are known.

If we now turn our attention to the ethynyl thioethers, we must first consider the influence exerted by an SR group on the reactivity of a conjugated organic molecule. There are several indications (83,140) that, owing to the ability of the sulfur atom on one hand to share its lone pairs of electrons with electron deficient groups and on the other hand to accommodate a decet of electrons in its valence shell, the SR group can act as an electron donor or as an acceptor according to the requirements of the reaction (83,131). The orientation observed during addition reactions to ethynyl thioethers is thus determined by the type of reaction involved. Electrophilic (electron-deficient) reagents will invoke electron release from the SR group and therefore will become attached to the β-carbon atom; nucleophilic reagents, by inducing the reverse polarization, also become attached to the β-carbon atom.



Polarization of ethynyl thioethers during reactions with electrophilic reagents. *Orientation to* β.



Polarization of ethynyl thioethers during reactions with nucleophilic reagents. *Orientation to* β.

Summarizing, we can state that the behavior of ethynyl oxygen ethers and of ethynyl thioethers toward electrophilic reagents is qualitatively the same, since in both cases the electrophilic group becomes attached to the β-carbon atom.

Nucleophilic reagents, however, will add to the α-carbon atom of ethynyl oxygen ethers and to the β-carbon atom of ethynyl thioethers.

B. REACTIONS OF THE ETHYNYLIC HYDROGEN ATOM

1. Metallation. The ethynylic hydrogen atom of ethynyl ethers and thioethers is easily replaceable by heavy metals. The silver salts are obtained as black or white precipitates by treatment with an ammoniacal solution of silver nitrate; the cuprous salts are yellow or orange powders formed by treatment with a solution of cuprous chloride in ammonia. Cuprous ethoxyethynylide soon decomposes in contact with the ammoniacal solution. If immediately filtered, washed, and dried, it can be kept for some time (37).

The mercuric derivatives of ethynyl thioethers, $Hg(C{\equiv}CSR)_2$, obtainable by means of a solution of mercuric iodide in aqueous potassium hydroxide (4,5), are beautifully crystalline solids (43).

Metallic derivatives of ethynyl compounds useful for synthetic applications are readily formed by reaction with Grignard or lithium compounds, usually in ethereal solution.

$$HC{\equiv}CXR + C_2H_5MgBr \longrightarrow BrMgC{\equiv}CXR + C_2H_6$$

$$HC{\equiv}CXR + C_6H_5Li \longrightarrow LiC{\equiv}CXR + C_6H_6$$
$$X = O \text{ or } S$$

The Grignard derivatives form oily complexes insoluble in ether but soluble in benzene. The lithium analogs are ether soluble to a certain extent; in concentrated solutions they sometimes separate as white powders.

The exchange reactions are performed at room temperature. (At too low temperatures the rates may be low. Newman and Kahle (169) report that butyllithium cannot be used for the conversion of ethoxyethyne into the lithium derivative. Their attempted reaction was carried out at $-10°$C., however. At room temperature the desired reaction would probably occur.) Completion of the conversion is indicated by termination of the evolution of hydrocarbon gas. At 25° this occurs in a few minutes.

The sodium derivative of phenoxyethyne has also been obtained by direct reaction of the ethynyl ether with finely divided sodium in ether (1,21,31). The sodium derivative of ethoxyethyne, prepared from *cis*- or *trans*-ethyl β-chlorovinyl ether with sodamide in liquid ammonia, is of considerable preparative importance because the solution can be used directly for reactions with carbonyl compounds

(34). Similarly, the lithium or sodium derivatives of the thioethers are obtained from the bromo ethers, CHBr=CHSR (37,42,43,178).

$$ClCH{=}CHOC_2H_5 + 2NaNH_2 \longrightarrow NaC{\equiv}COC_2H_5 + 2NH_3 + NaCl$$

Ethoxyethynylsodium is also formed from chloroacetal and sodamide in liquid ammonia (33) (see Section II-A-2), but the resulting solution cannot be satisfactorily used for reactions with carbonyl compounds because it now contains sodium ethoxide (33).

The preparation of ethoxyethynylsodium from ethyl α,β-dibromo- or- dichloroethyl ether and three moles of sodamide in liquid ammonia followed by reaction with butyl bromide and hydration of the ethoxyhexyne formed has been reported (17), but the yield of the end product was low.

Note: For best results, the liquid ammonia used in the above reactions must be anhydrous (37). The commercial material in cylinders contains small amounts of moisture and reactions performed in this solvent may give low yields. Satisfactory purification is achieved by pouring the liquid from the cylinder, adding small pieces of metallic sodium until the blue color persists, and distilling the liquid into the carefully dried, cooled reaction flask.

A convenient method for the preparation of the lithium derivatives of (aryl(and alkyl)thio)ethynes consists of the reaction of bis(alkyl(or aryl)thio)ethenes (4,44) with butyllithium in ether (Section II-C-3). The sodium derivative of (ethylthio)ethyne is best prepared from 1,2-bis(ethylthio)ethene and sodamide in liquid ammonia (176).

2. Use of Metallic Derivatives. (The very important use of metallic derivatives for the syntheses of ethoxy- and (ethylthio)ethynylcarbinols is treated in Section III-C.) Some metal derivatives of ethynyl ethers and thioethers have been used for the synthesis of alkylated products of the type $RC{\equiv}CXR'$ (X = O or S). Thus, 1-phenoxy-1-butyne and 1-phenoxy-1-hexyne are obtained from phenoxyethynylmagnesium bromide and ethyl or butyl *p*-toluenesulfonate in ether (21).

$$BrMgC{\equiv}COC_6H_5 + CH_3\text{—}C_6H_4\text{—}SO_2OR \longrightarrow RC{\equiv}COC_6H_5 + CH_3\text{—}C_6H_4\text{—}SO_2OMgBr$$

Considerable amounts of phenol are also formed.

1-Phenoxy-1-propyne is the product of the condensation of the sodium derivative of phenoxyethyne with methyl iodide in liquid ammonia (31), and 1-phenylthio-1-propyne has been obtained from (phenylthio)ethynyllithium and dimethyl sulfate in ether (4). Similarly, 1-ethylthio-1-alkynes arise from (ethylthio)ethynylsodium and alkyl halides in liquid ammonia (176). Ethoxyethynylsodium and trimethylene bromide in liquid ammonia give $C_2H_5OC{\equiv}C(CH_2)_3C{\equiv}COC_2H_5$ in reasonable yield (177).

Ethoxyethynyllithium and epichlorohydrin react mainly as follows (178):

$$\underset{\diagdown\,\diagup\ \ \ \

$$LiC{\equiv}CXC_2H_5 \xrightarrow{C_6H_5N=C=O} C_6H_5NHC(=O)C{\equiv}CXC_2H_5$$

Products are stable when X = S, highly unstable when X = O.

The sodium or Grignard derivatives of phenoxyethyne react with benzoyl chloride to yield phenylbenzoate as the main product (3), and not 1-phenoxy-3-phenylprop-1-yne-3-one as reported earlier (1). However, (ethylthio)ethynyllithium and acetic anhydride give 45% of 1-(ethylthio)but-1-yne-3-one in ether at −20°C. (198).

3. Substitution of the Ethynyl Hydrogen Atom by Halogens. Generally an ethynylic hydrogen atom is substituted by halogen when the Grignard derivative is treated with free halogen (especially iodine) or when the ethynyl compound reacts with a hypohalite. Conversions of this type have been studied only with phenoxyethyne (41) and ethoxyethyne (37). The attempts were not fully successful, undoubtedly because of the pronounced instability of the halogenated ethynyl ethers.

1-Bromo-2-phenoxyethyne, obtained in impure condition by the action of an alkaline potassium hypobromite solution on phenoxyethyne, polymerized very readily, sometimes explosively (41). The corresponding iodo derivative could not be prepared; triiodophenoxyethene was invariably the main product (41).

Impure 1-iodo-2-ethoxyethyne was one of the products obtained by interaction of ethoxyethynylmagnesium bromide with iodine in ether, or of ethoxyethyne with a solution of potassium iodide and sodium hypochlorite in water (37).

The halogenated ethynyl ethers are readily converted into haloacetates by acid hydration.

$$XC{\equiv}COR \xrightarrow[H^+]{H_2O} XCH_2COOR$$

X = Cl or Br

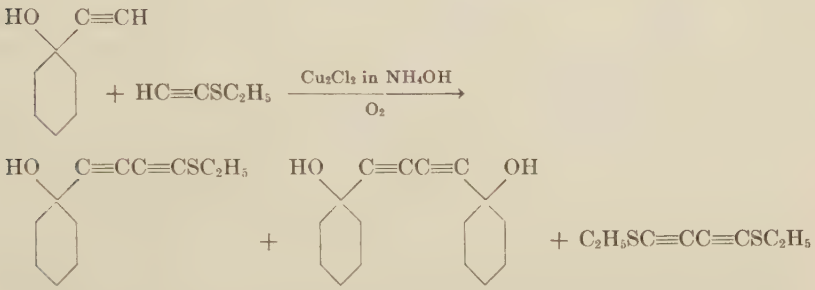
4. Oxidative Coupling of Ethynyl Thioethers. Oxidation of the cuprous salt of (ethylthio)- or (*tert*-butylthio)ethyne to the corresponding butadiynylene bisthioethers has been accomplished with oxygen (20).

$$C_2H_5SC{\equiv}CH \xrightarrow[O_2]{Cu_2Cl_2 \text{ in } NH_4OH} C_2H_5SC{\equiv}CC{\equiv}CSC_2H_5$$

The products are rather unstable and may undergo vigorous decomposition upon heating.

A mixed coupling product can be obtained by similar treatment of

a mixture of an ethynyl thioether and another ethynyl compound, although both symmetrical butadiynes are formed at the same time (37).



A successful oxidative coupling of two molecules of ethoxyethyne could not be effected; only black smears were obtained. Very careful attempts, including oxidation of the isolated cuprous salt with hydrogen peroxide or potassium ferricyanide, did yield a product, but this decomposed vigorously at 30° (37).

5. Mannich Reactions. Several compounds possessing an ethynylic hydrogen atom have been reported to undergo "Mannich reactions" with formaldehyde and primary or secondary amines (113), although not very easily.

$$R_2NH + CH_2O + HC{\equiv}CR' \longrightarrow R_2NCH_2C{\equiv}CR'$$

Similar attempts with ethoxyethyne do not yield Mannich bases but β-amino esters. These conversions, which must be considered not as Mannich reactions but as electrophilic additions to the triple bond, are treated in Section III-D-7. A true Mannich reaction can be effected between (ethylthio)ethyne, formaldehyde, and diethylamine in boiling dioxane. The product, $(C_2H_5)_2NCH_2C{\equiv}CSC_2H_5$, is obtained in almost quantitative yield (176).

The failure of ethoxyethyne to undergo Mannich reactions may be due to the negative character of the β-carbon atom. This hinders the dissociation of the ethynylic hydrogen atom as a proton, a necessary condition for the Mannich reaction.

C. PREPARATION AND APPLICATIONS OF ALKOXY- AND (ALKYLTHIO)ETHYNYLCARBINOLS

1. Alkoxyethynylcarbinols. The most important use of metallated ethynyl ethers is for the synthesis of carbinols by reaction with carbonyl compounds (21) (see Table III).

$$RR'C{=}O + MC{\equiv}COC_2H_5 \longrightarrow$$
$$RR'C(OM)C{\equiv}COC_2H_5 \xrightarrow[H_2O\ (M\ =\ Na\ or\ Li)]{NH_4Cl\ (M\ =\ MgBr)} RR'C(OH)C{\equiv}COC_2H_5$$

These carbinols are versatile synthetic intermediates and will be discussed in some detail. A few words might be in order at this point about their preparation.

Many authors perform the condensation of ethoxyethynylmagnesium bromide with ketones by refluxing the ethereal solutions (sometimes diluted with benzene to achieve a homogeneous system) for several hours. In the author's opinion, refluxing is unnecessary and even harmful. Brown colors easily develop and the yields diminish. Generally the coupling reactions are sufficiently fast to allow operations at a low temperature (−20°). In this way side reactions, such as aldol formation from the carbonyl compound, are avoided, and only slightly colored reaction products are obtained in satisfactory yield. In some cases the complex $RR'C(OMgBr)C{\equiv}COC_2H_5$ separates directly from the reaction mixture as a sandy precipitate.

In view of the extreme sensitivity of ethoxyethynylcarbinols to acids, the reaction mixtures must be worked up by pouring into a cold solution of ammonium chloride or, if the lithium or sodium derivatives are used, into cold water. The carbinols must be distilled as soon as possible after short drying. If the distillations are postponed, vigorous decompositions may occur, partly due to the formation of traces of acids which cause rearrangement (cf. Section III-C-3; however, see also Section III-H-1). The distillations should be performed at as low a temperature as possible. It is often advantageous to use the undistilled products.

The Grignard derivatives of ethoxyethyne usually cannot be employed for the preparation of *secondary* carbinols from aldehydes (84) because these compounds react further with the initially formed magnesium bromide carbinolates (see Section III-D-7). (Bohlmann, Ahrens, and Kritzler (161), however, prepared $(CH_3)_3CCH(OH)$-$C{\equiv}COC_2H_5$ from trimethylacetaldehyde and ethoxyethynylmagnesium bromide in good yield.) Such complications are avoided by using ethoxyethynyllithium in ether (85) or the sodium derivative in liquid ammonia (34), provided that the aldehyde is stable to ammonia. A recommended general procedure for the synthesis of ethoxyethynylcarbinols consists of the reaction of carbonyl compounds with ethoxyethynyllithium in ether or ether–benzene.

A few carbinols have been prepared by direct interaction of a carbonyl compound, free ethoxyethyne, and potassium hydroxide (171). This procedure is often employed for the synthesis of carbinols from ethyne itself (111).

2. (Alkylthio)ethynylcarbinols. Carbinols derived from aliphatic ethynyl thioethers have been prepared (in close analogy to their oxygen analogs) from ketones as well as from aldehydes (20,44). It is noteworthy that the bromomagnesium derivatives of (alkylthio)-ethynes give good results with both ketones and aldehydes (20,37).

The preparation of (alkylthio)ethynylcarbinols by interaction of carbonyl compounds with metal derivatives of alkylthioethynes formed from 1,2-bis(alkylthio)ethenes with butyllithium in ether (44) or with sodamide in liquid ammonia (176) is very convenient (cf. Section II-C-4).

$$C_4H_9Li + RSCH{=}CHSR \longrightarrow LiC{\equiv}CSR \longrightarrow R'R''C(OH)C{\equiv}CSR$$

3. Rearrangement of Alkoxyethynylcarbinols. Ethoxyethynylcarbinols have found two major uses, viz., for the preparation of α,β-unsaturated esters and of α,β-unsaturated aldehydes.

α,β-Unsaturated esters are formed by rearrangement of ethoxyethynylcarbinols in the presence of dilute acids (13–15,27,85,88–101,112,114,115,143,154,161,171).

$$\begin{array}{c} \diagdown \\ \diagup \end{array}\!\!\overset{\displaystyle OH}{\underset{|}{C}}C{\equiv}COC_2H_5 \xrightarrow[H_2O]{H^+} \begin{array}{c} \diagdown \\ \diagup \end{array}\!\!C{=}CHCOOC_2H_5 + \begin{array}{c} \diagdown \\ \diagup \end{array}\!\!\overset{\displaystyle OH}{\underset{|}{C}}CH_2COOC_2H_5$$

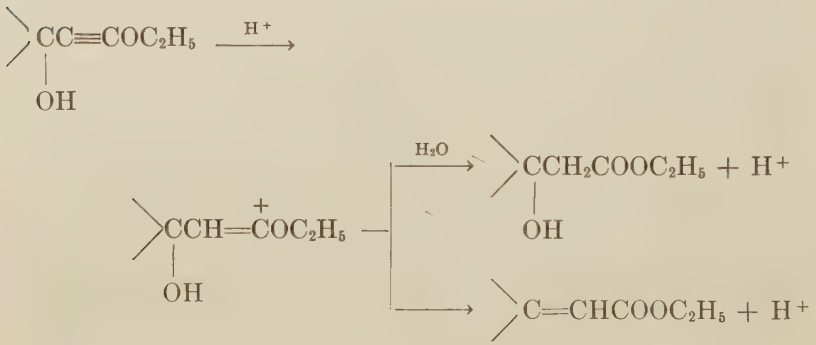
Recommended procedures for the conversions are treatment of solutions of the carbinols in alcohol, dioxane, or tetrahydrofuran with small amounts of 10% aqueous sulfuric acid at room temperature for $^1/_4$-2 hr., or shaking of ethereal solutions with aqueous 10% sulfuric acid at room temperature for 15 min.

The α,β-unsaturated esters are usually the main products, but occasionally mixtures of the unsaturated and the β-hydroxy esters are formed; sometimes the latter are the main products. The results obtained are influenced by the solvent, but no clear rules can be deduced from the available data.

The formation of unsaturated esters is primarily a rearrangement, not a hydration followed by elimination of water, because the reaction conditions are too mild for such eliminations (cf. refs. 92,100a,100b).

The contaminating β-hydroxy esters are probably the products of such a hydration. The ratio of the two ester types is presumably determined by the relative rates of the two types of reaction.

Sarett and co-workers (100b) express the opinion that the formation of both the hydroxy ester and the unsaturated ester is preceded by proton addition. The resulting carbonium ion either reacts with water to yield the hydroxy ester or undergoes a 1,3-shift forming the unsaturated ester.



Some carbinols (especially in polycyclic systems related to the steroids, with the ethoxyethynyl group attached to a six-membered ring) are somewhat resistant to rearrangement and need prolonged treatments with solutions of sulfuric acid in dioxane or tetrahydrofuran (101). The resistance may be due to an increase of internal strain in the rearranged product because of deformation of bond angles by the exocyclic double bond (cf. ref. 102).

It is possible to effect rearrangements under anhydrous conditions by refluxing with nitroanilines in alcohol (99b).

Some ethoxyethynylcarbinols are so sensitive to traces of acids that rearrangement occurs during attempted distillation from Pyrex flasks cleaned with nitric or chromic acid. In order to obtain pure carbinols, the flasks must be rinsed with alkali prior to drying.

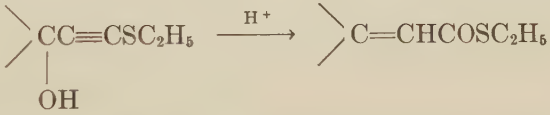
One case is reported (115) where spontaneous rearrangement of a carbinol took place by dissolution in methanol. This must have been

caused by the presence of traces of acid, however; the observation could not be reproduced (37).

The rearrangements generally do not yield sterically homogeneous unsaturated esters. There are indications that the predominating compounds have *cis* configurations (27,90,94,97; in particular 169), although in some cases the *trans* acids have been isolated (85). It has not been investigated whether these *trans* acids may have arisen by isomerization of the *cis* esters during alkaline saponification.

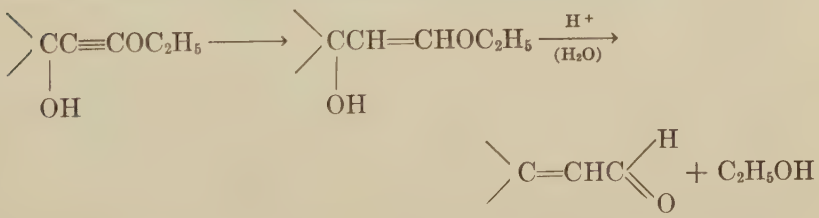
Probably this method for the preparation of α,β-unsaturated esters will be ousted by the much easier direct conversion of carbonyl compounds with ethynyl ethers under the influence of boron fluoride (180) (cf. Section III-D-7).

4. Rearrangement of (alkylthio)ethynylcarbinols. Treatment of (alkylthio)ethynylcarbinols with acids gives satisfactory yields of α,β-unsaturated thiol esters. This seems to be a general method for the preparation of these substances, although not many examples are described (20).



Here, too, it will be easier to prepare the α,β-unsaturated thioesters directly from carbonyl compound and (alkylthio)alkyne with boron fluoride (176; cf. Section III-D-7).

5. α,β,-Unsaturated Aldehydes from Alkoxyethynylcarbinols. The second major application of ethoxyethynylcarbinols, as already indicated in the historical section, is for the preparation of α,β-unsaturated aldehydes (9,11–13,15,27,34,88,89,101,103–108,110,112,114–116,171).



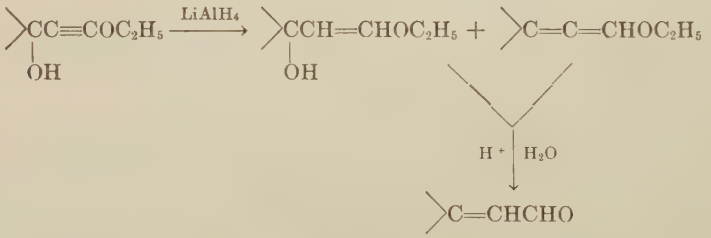
Good yields are obtained. (Also, α-ethylthio α,β-unsaturated aldehydes can be prepared from ethoxyethynylcarbinols. This is discussed in Section III-F-1.)

The partial reduction of the triple bond is usually performed with hydrogen and a palladium catalyst on barium sulfate, calcium carbonate, or carbon. Care must be taken to interrupt the reduction after the absorption of one mole of hydrogen; otherwise, the saturated ether may be obtained. The method is applicable even to carbinols derived from highly unsaturated aldehydes and ketones and has been used for the synthesis of all-*trans* and of a *cis* vitamin A aldehyde (12,103,104).

Catalytic reduction with partly deactivated palladium, e.g., with the Lindlar catalyst (109) in the presence of quinoline (34) or with 10% Pd-$CaCO_3$ in pyridine (101,106), is advantageous because this hydrogenation stops after absorption of one mole of hydrogen; there is thus little danger of overreduction.

Sometimes the catalytic reductions start with difficulty. Repeated addition of new catalyst is then necessary.

Reductions can also be performed with an excess of a clear, filtered solution of lithium aluminum hydride in ether at room temperature, but then in addition to the ethoxyvinylcarbinols allenyl ethers are also obtained. This also applies to reductions with diisobutylaluminum hydride (190).



A peculiar reduction by means of hydrazoic acid (116) is discussed in Section III-D-2.

In the steroid series one case is reported where partial catalytic reduction of the triple bond in an axial α-position could not be effected without reduction of a double bond elsewhere in the molecule (112). It is interesting to note that partial reduction of the isomer having the $C{\equiv}COC_2H_5$ group in the equatorial β-position was possible.

Conversion of the ethoxyvinylcarbinols into the desired α,β-unsaturated aldehydes is usually facile. Shaking of an ethereal solution for a short time with dilute aqueous acid at room temperature is often sufficient. This makes the method attractive because other sensitive

portions of the molecule are not attacked. In the steroid series, for instance, a 3-keto group protected as a ketol with ethylene glycol usually remains ketalized.

Some cases were encountered, however (101,112), where such ethoxyvinylcarbinols were resistant to rearrangement under mild conditions. Somewhat more drastic conditions resulted in hydrolysis of the 3-ketal rather than the ethoxyvinyl group. Fortunately, such compounds could be rearranged readily into the α,β-unsaturated aldehyde at room temperature with phosphorus tribromide or thionyl chloride, preferably in the presence of pyridine (101,112,165).

The prolonged treatments with hot acids sometimes reported (9,13) are quite unnecessary and harmful. Some reports (9,13) stating that reaction of the γ-hydroxyvinyl ethers with carbonyl reagents like 2,4-dinitrophenylhydrazine yields derivatives of β-hydroxy aldehydes rather than of α,β-unsaturated aldehydes are not convincing. We always obtained good yields of the α,β-unsaturated derivatives, even at room temperature, by treatment of ethoxyvinylcarbinols with a solution of 2,4-dinitrophenylhydrazine in sulfuric acid and alcohol.

The aldehydes, obtained by the methods discussed, appear to be mixtures of the *cis* and *trans* isomers (27,34,107).

It remains to be investigated whether the configuration of the product can be influenced by the nature of the previous reduction. Thus, catalytic hydrogenations produce mainly *cis*, and lithium aluminum hydride reductions *trans*, dihydro products, and these isomers may give rise to different amounts of *cis* and *trans* α,β-unsaturated aldehydes.

Also, (alkylthio)ethynylcarbinols have been converted into α,β-unsaturated aldehydes by partial reduction (with lithium aluminum hydride) and subsequent treatment with acid (20). Here, too, the yields are satisfactory.

D. ADDITIONS OF ELECTROPHILIC REAGENTS TO THE TRIPLE BOND

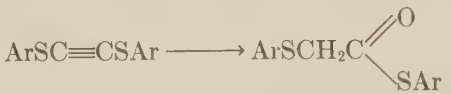
1. Acid-Catalyzed Hydration. The most conspicuous property of ethynyl alkyl ethers is their very easy and quantitative hydration to esters by shaking with dilute mineral acids (3,24,25). With strong acids, such as 5*N* hydrochloric acid, the conversion proceeds with almost explosive violence.

$$HC{\equiv}COC_2H_5 + H_2O \xrightarrow{H^+} H_3CCOOC_2H_5$$

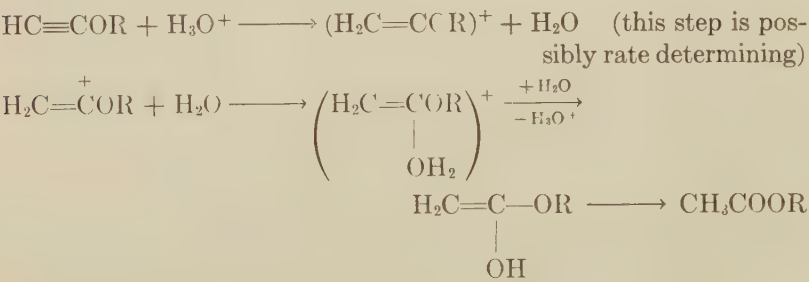
Alkylated and arylated derivatives of the type RC≡COR′, as well as phenoxyethyne, react readily but at a slower rate (17,21,29,32). In some cases mercuric oxide or acetate has been added as catalyst (3,17).

(Ethylthio)ethyne and (ethylthio)propyne are less easily hydrated (37,182). The second order rate constant for the hydration of (ethylthio)ethyne is 10^3-10^4 lower than that for the corresponding reaction of ethoxyethyne (199).

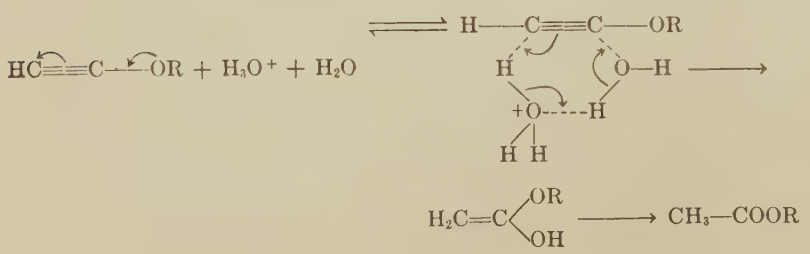
1,2-Bis(arylthio)ethynes are hydrated when warmed with 50% sulfuric acid in acetic acid (71). (The yield was not mentioned.)



Jacobs and Searles (117) have measured the rates of the acid-catalyzed hydration of ethoxy-, butoxy-, and phenoxyethynes in aqueous alcoholic solution at 25° by a dilatometric method. The reactions are first order with respect to ethynyl ether and hydrogen ion concentration. The observed kinetics are consistent with the following mechanism (117).



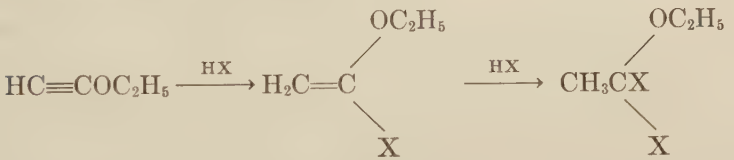
However, a concerted mechanism would likewise be satisfactory.



The ease with which this acid-catalyzed hydration takes place is a reflection of the electron-donating properties of the OR group. The slower hydration of (ethylthio)ethyne is a result of the weaker electron-donating effect of the SR group.

The very slow *base*-catalyzed hydration of ethynyl ethers will be discussed in the section on nucleophilic additions (Section III-E-3).

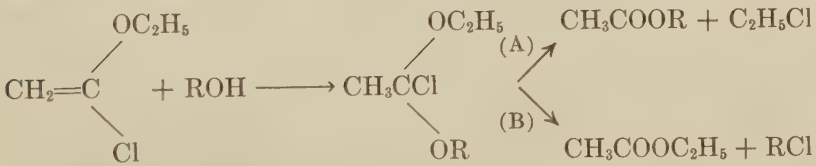
2. Additions of Hydrogen Halides and of Hydrazoic Acid. Ethoxyethyne readily adds anhydrous hydrogen halides in ethereal solution. If equimolar amounts are used, satisfactory yields of ethyl α-halogenovinyl ethers are obtained (for Cl see refs. 24,118,119; for Br see ref. 122). The substances can react with a second molecule of hydrogen halide giving ethyl α,α-dihalogenoethyl ethers (120,122), also obtainable in one operation from ethoxyethyne. The products are mobile, colorless liquids with pungent odors.



X = Cl or Br

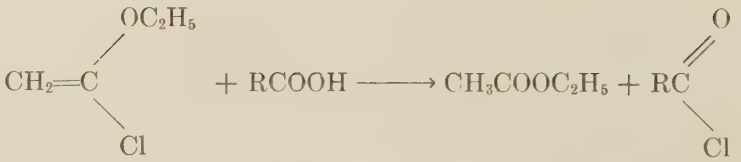
The addition of hydrogen chloride to (ethylthio)ethyne yields 1-chloro-1-(ethylthio)ethene (176).

Ethyl α-chlorovinyl ether reacts vigorously with water (24,118) yielding ethyl acetate and hydrogen chloride. It converts anhydrous alcohols and phenols into chlorides and/or acetates (118).



A is the main reaction when R = phenyl, β-naphthyl, cyclohexyl; B is the main reaction when R = trityl, benzyl.

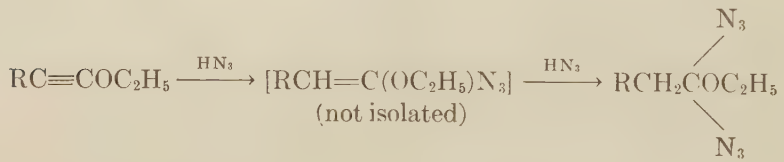
Toward dry sodium ethoxide, ethyl α-chlorovinyl ether is unreactive (24). The reaction with carboxylic acids leads to the formation of acid chlorides (formic acid decomposes to carbon monoxide) (121).



An excellent reagent for acid chloride formation is ethyl α,α-dichloroethyl ether, which gives high yields and very smooth reactions (120).

$$CH_3C(OC_2H_5)Cl_2 + RCOOH \longrightarrow CH_3COOC_2H_5 + RCOCl + HCl$$

Interesting diazido ethers are obtained from ethoxyethyne or 1-ethoxy-1-propyne and anhydrous hydrazoic acid dissolved in benzene (116,123).



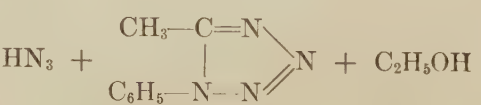
$$R = H \text{ or } CH_3$$

The monoadduct 1-azido-1-ethoxyethene $CH_2{=}C(OC_2H_5)N_3$ can be prepared in methylene chloride in the presence of mercuric acetate (183).

Nucleophilic reagents can replace one or two of the azido groups of the explosive diazide to yield a variety of products as shown in the following formula schemes (116,123,125).

$$CH_3C(OC_2H_5)(N_3)_2 + 2NaOC_2H_5 \longrightarrow 2NaN_3 + CH_3C(OC_2H_5)_3$$

$$CH_3C(OC_2H_5)(N_3)_2 + 2NaSC_2H_5 \longrightarrow 2NaN_3 + CH_3C(OC_2H_5)(SC_2H_5)_2$$



$$CH_3C(OC_2H_5)(N_3)_2 + 2RNH_2 \longrightarrow 2HN_3 + CH_3C(=NR)NHR + C_2H_5OH$$

$$CH_3C(OC_2H_5)(N_3)_2 + 2C_2H_5SH \longrightarrow$$

$$(C_2H_5S)_2 + CH_3{-}C{=}N\diagdown\!\!\diagup N + C_2H_5OH$$

$$\qquad\qquad\qquad\qquad\qquad\qquad\quad HN{-}N{=}\diagup$$

$$CH_3C(OC_2H_5)(N_3)_2 + (C_6H_5)_2NH \longrightarrow$$

$$HN_3 + CH_3C(=O)N(C_6H_5)_2 + C_2H_5N_3$$

(For an explanation of these conversions consult ref. 116.)

Another noteworthy conversion was observed by heating 1,1-diazido-1-ethoxyethane with acetic or propionic acid (116,125). This yielded—among other products—the ethyl ester of *N*-acetyl- or *N*-propionylglycine.

$$CH_3C(OC_2H_5)(N_3)_2 + RCOOH \longrightarrow$$

$$RCONHCH_2COOC_2H_5 + N_2 + HN_3$$

This result has not yet been explained in a satisfactory manner.

An unusual reaction of 1,1-diazido-1-ethoxyethane occurs upon gentle heating with hydrazoic acid. Evolution of nitrogen is observed and from the dark product 1-azido-1-ethoxyethane can be isolated. Obviously this is a "reduction" by hydrazoic acid (116).

$$CH_3C(OC_2H_5)(N_3)_2 + HN_3 \longrightarrow 3N_2 + CH_3CH(OC_2H_5)N_3$$

This reaction has been utilized for the conversion of ethoxyethynylcarbinols into α,β-unsaturated aldehydes in satisfactory yield (116).

$$RR'C(OH)C{\equiv}COC_2H_5 + 2HN_3 \longrightarrow$$

$$[RR'C(OH)CH_2C(OC_2H_5)(N_3)_2] \xrightarrow{HN_3}$$

(not isolated)

$$3N_2 + RR'C(OH)CH_2CH(OC_2H_5)N_3 \xrightarrow[H^+]{H_2O}$$

(isolated)

$$HN_3 + C_2H_5OH + RR'C{=}CHCHO$$

3. Addition of Alcohols and Phenols Catalyzed by Boron Fluoride. Most alcohols and phenols (with the exception of such substances as picric acid) are not sufficiently acidic to undergo uncatalyzed addition to ethoxyethyne. Their acidity can be increased, however, by addition of boron fluoride, occasionally combined with mercuric oxide, and under these conditions addition occurs readily (3). The catalyst,

however, converts ethoxyethyne into a polymer and the yields are therefore rather unsatisfactory.

Ethyl acetate is obtained from ethoxyethyne (3), probably via the intermediate formation of ethyl orthoacetate which is known to eliminate ether upon treatment with boron fluoride (126).

$$HC{\equiv}COC_2H_5 + C_2H_5OH \xrightarrow{BF_3}$$

$$[H_2C{=}C(OC_2H_5)_2 \xrightarrow{C_2H_5OH} H_3CC(OC_2H_5)_3] \xrightarrow{BF_3}$$

(not isolated)

$$CH_3COOC_2H_5 + C_2H_5OC_2H_5$$

Keteneacetal, postulated as the first intermediate, has not been isolated. This is not surprising in view of the fact that this substance reacts rapidly with alcohol (128,128a).

If alcohols other than ethanol are used, the intermediate mixed orthoacetate may decompose by path A or path B. Since the main products found are the acetate and ethyl ether of the alcohol (or phenol) used, reaction A seems to be preferred (127).

$$HC{\equiv}COC_2H_5 + 2ROH \xrightarrow{BF_3}$$

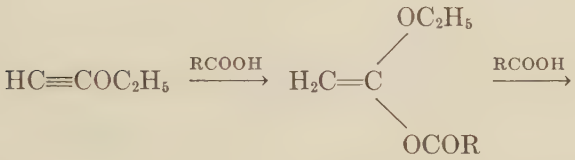
$$\left[H_3CC(OR)_2OC_2H_5 \right] \xrightarrow{BF_3} \begin{cases} \xrightarrow{(A)} CH_3COOR + ROC_2H_5 \\ \xrightarrow{(B)} CH_3COOC_2H_5 + ROR \end{cases}$$

Addition of alcohol to ethoxyheptyne in the presence of $BF_3 \cdot HgO$ gives ethyl heptylate in 82% yield (29).

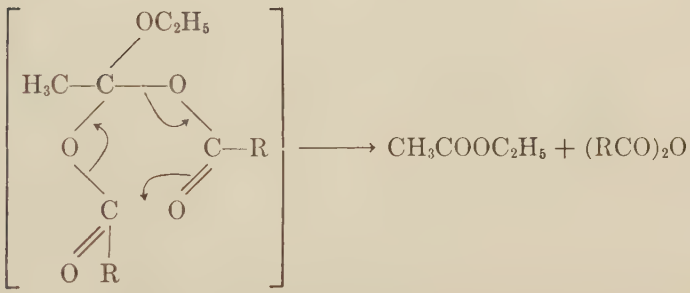
The addition of alcohols in the presence of base (127) is discussed in the section on nucleophilic additions (Section III-E-3).

4. Reaction of Alkoxyalkynes with Hydroxylic Acids. When the hydrogen atom of an OH group becomes sufficiently acidic, the substance can interact spontaneously with ethynyl ethers. This is the case for carboxylic, sulfonic, and phosphoric acids. Both mercuric oxide and phosphoric acid have been used to catalyze the reaction

with weak carboxylic acids (17); the use of phosphoric acid cannot be recommended, however, because it reacts with ethoxyethyne itself. The ultimate product is the anhydride of the acid used (16,17,29,129).



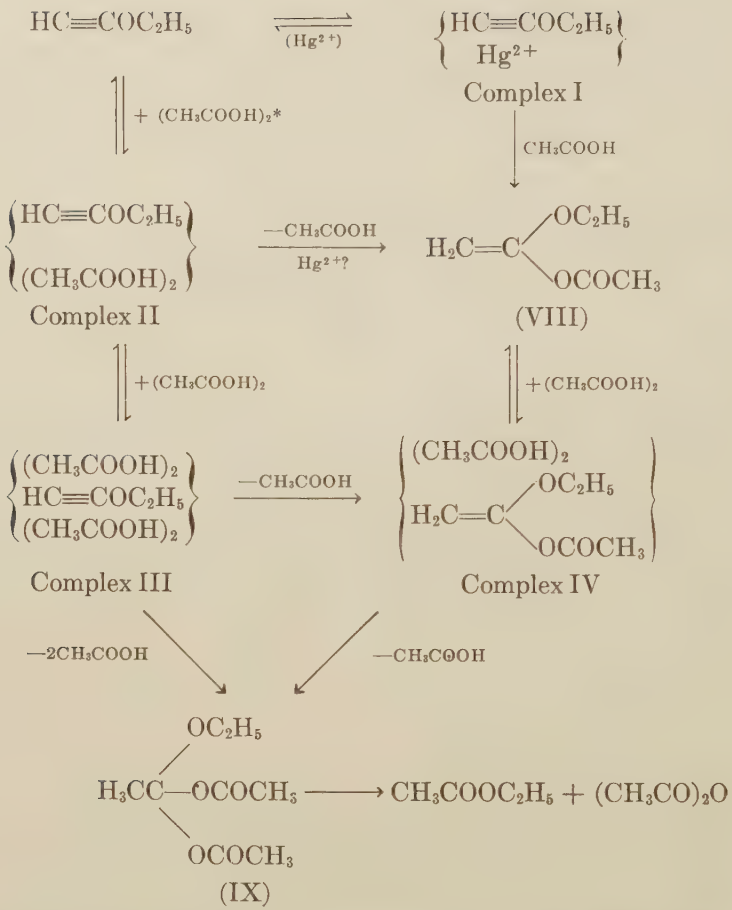
(VIII)



(IX)
(not isolated)

The monoadduct (VIII) has been isolated from trichloroacetic acid (122) and from some other acids containing a strongly negative group R (37). Monoadducts of other carboxylic acids can be obtained if mercuric salts are present (172). The substances readily react with acid to yield anhydride (122,172). Evidence for the occurrence of the intermediate (IX) has been acquired by means of O^{18}-labeled acids (172).

On the other hand, a preliminary kinetic investigation of the reaction between ethoxyethyne and acetic acid in benzene indicated that the rate of disappearance of ethoxyethyne is proportional to the concentration of ethoxyethyne and to the square of the concentration of acetic acid (193). This can hardly be brought into line with the occurrence of intermediate VIII. Possibly the reactions take one of the following alternative paths.



The over-all kinetics depend on the relative rates of the several steps. These, in turn, determine whether or not VIII will be an intermediate product. Mercuric ions possibly catalyze the irreversible transformation of complex II into VIII or give rise to the formation of VIII via complex I.

This very mild method for the synthesis of acid anhydrides is generally applicable; good yields are obtained from aliphatic and aromatic carboxylic and sulfonic acids even at low temperatures. The previously unknown anhydride of the sensitive vinylacetic acid

* In benzene acetic acid is present in the dimeric state.

has been prepared in this manner (37); other methods appear to yield the isomeric crotonic anhydride.

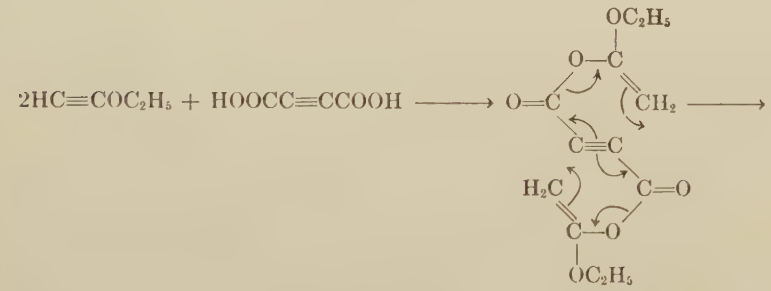
Diethyl phosphate smoothly reacts to yield tetraethyl pyrophosphate (129). Formic acid is converted into carbon monoxide (16) even at 0° (17), and oxalic acid is converted into carbon monoxide and carbon dioxide (17). Malonic acid yields a sirupy product, the exact nature of which is not known with certainty (17), and succinic acid gives the intramolecular anhydride.

1-Ethoxy-1-alkynes can also convert acids into anhydrides (29), but heating is required.

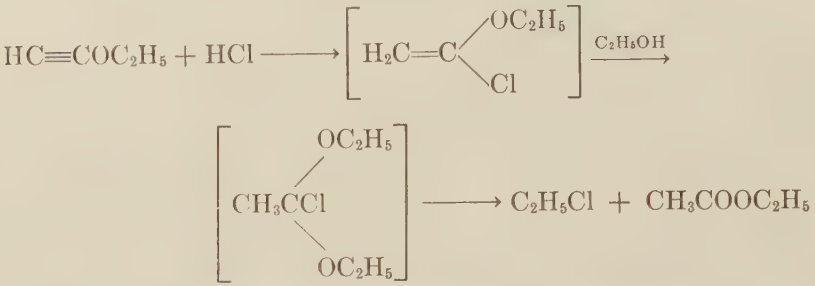
If the acidity of an acid is not due to an OH group, no reaction takes place. Thus, tetraethyl pyrophosphite cannot be prepared from diethyl phosphite (129).

Trichloroacetic anhydride can be obtained from trichloroacetic acid only if the calculated amount of ethoxyethyne is slowly added to the solid acid at 0° (122). Excess ethoxyethyne reacts rapidly with the anhydride (122) (see Section III-G-3).

Phenylpropiolic acid is converted into 1-phenylnaphthalene-2,3-dicarboxylic anhydride (179), which is probably the product of ring closure of the anhydride of phenylpropiolic acid. A very peculiar reaction occurs between butynedioic acid and ethoxyethyne in alcohol. The racemic form of the ethyl ester of butane-1,2,3,4-tetracarboxylic acid is obtained, probably as the result of a rearrangement of the primary adduct (179).



5. Esterification of Mixtures of Acids and Alcohols by Alkoxyethynes. Ethyl chloride and ethyl acetate are formed when ethoxyethyne is added to alcoholic hydrogen chloride (24).



Probably ethyl α-chlorovinyl ether is an intermediate (see Section III-D-2).

Propoxyethyne, propanol, and hydrogen chloride similarly yield propyl chloride and propyl acetate (24), whereas ethoxybutyne, ethanol, and hydrogen chloride are converted into ethyl chloride and ethyl butyrate (25).

Carboxylic esters are formed by warming a mixture of alcohol, acid, and ethoxyethyne (37). Here very probably the acid is first transformed into its anhydride as discussed in Section III-D-4, whereupon the anhydride reacts with the alcohol. Although excellent results are obtained with primary alcohols, the reaction with tertiary alcohols is unsatisfactory.

6. Amide Formation between Acids and Amines by Alkoxyethynes; Preparation of Peptides. Methoxyethyne has been used for the conversion of mixtures of acids and amines into amides (18).

A convenient synthesis of peptides, based on this principle (19,163), consists in refluxing an N-protected amino acid or peptide with an amino acid or peptide ester hydrochloride and excess of ethoxyethyne in moist ethyl acetate until the insoluble hydrochloride has disappeared. This generally requires 0.5–2 hr. The N-protecting group most often used is the benzyloxycarbonyl (Cb) group, but other derivatives are also satisfactory (19,163).

$$CbNHCHRCOOH + HCl \cdot H_2NCHR'COOC_2H_5 + HC{\equiv}COC_2H_5 \longrightarrow CbNHCHRCONHCHR'COOC_2H_5 + CH_3COOC_2H_5 + HCl$$

The hydrogen chloride liberated partly escapes through the reflux condenser and partly reacts with the excess of ethoxyethyne to yield ethyl α-chlorovinyl ether and ethyl α,α-dichloroethyl ether (see Section III-D-2).

These substances can be used for peptide syntheses under essentially the same conditions (119). The processes go by way of acid chlorides.

$$CbNHCHRCOOH + CH_2{=}C(OC_2H_5)Cl \text{ (or } CH_3C(OC_2H_5)Cl_2) \longrightarrow CbNHCHRCOCl + CH_3COOC_2H_5 \text{ (+ HCl)}$$

$$CbNHCHRCOCl + HCl \cdot H_2NCHR'COOCH_3 \longrightarrow CbNHCHRCONHCHR'COOCH_3 + 2HCl$$

Instead of ester hydrochlorides, the free amino acid or peptide esters can be used.

The mechanism of the peptide syntheses with ethoxyethyne is not completely clear. Possibly, as indicated in Scheme I, the anhydrides (XI) of the N-protected amino acids are formed first, probably via the ketene derivatives (X) (cf. Section III-D-4). Direct interaction of the amino component with X according to Scheme II must also be envisaged, however, especially when the strongly nucleophilic free amino acid esters are used.

Scheme I

$$CbNHCHRCOOH + HC{\equiv}COC_2H_5 \longrightarrow H_2C{=}C(OC_2H_5)(OCO{-}CHR{-}NHCb)$$

(X)

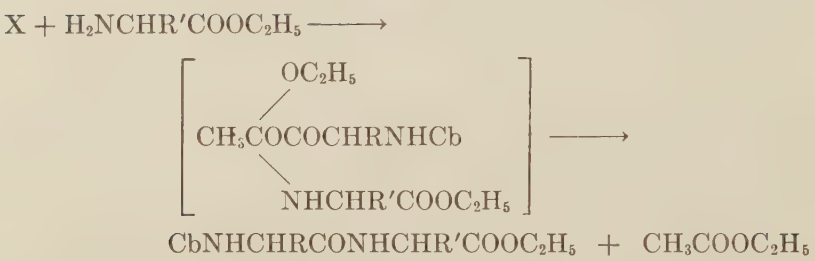
$$X + CbNHCHRCOOH \longrightarrow CH_3COOC_2H_5 + (CbNHCHRCO)_2O$$

(XI)

$$XI + H_2NCHR'COOC_2H_5 \cdot HCl \longrightarrow CbNHCHRCONHCHR'COOC_2H_5 + HCl +$$

CbNHCHRCOOH (is reconverted into anhydride etc.)

SCHEME II

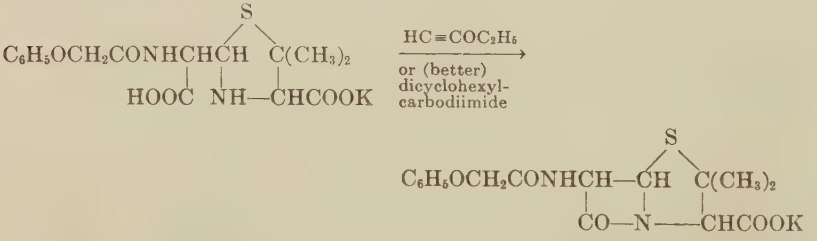


The intermediate corresponding to X derived from ethoxyethyne and phthalylglycine has been isolated by Sheehan and Hlavka and converted into a dipeptide with ethyl glycinate (164).

No racemization occurs during the synthesis of dipeptides by means of ethoxyethyne, but occasionally partial racemization has been observed during the synthesis of higher peptides when the hydrochlorides of the amino components were used. This complication can be avoided almost completely by working with the free amino components (163).

The special advantage of the ethoxyethyne method for peptide synthesis is the easy removal of the excess of the reagent and its transformation product, ethyl acetate.

According to Sheehan (130), ethoxyethyne can be used for closure of the four-membered ring of penicillin, but dicyclohexylcarbodiimide gives better results (130).

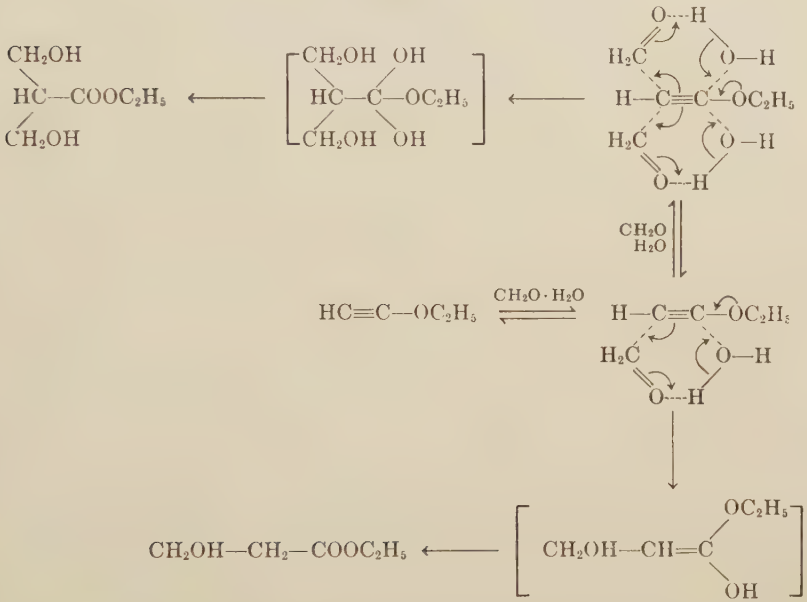


7. Reactions with Carbonyl Compounds. Neutralized aqueous formaldehyde reacts with ethoxyethyne to give ethyl 2-hydroxypropionate in 60% yield, together with a small amount of ethyl acrylate. From very concentrated formaldehyde solutions, a considerable amount of ethyl β-hydroxy-α-(hydroxymethyl)propionate is obtained as a second by-product. This by-product cannot be prepared from

the former compound under the same conditions and must therefore be formed simultaneously.

Scheme III explains the formation of both hydroxy esters (132).

SCHEME III



Analogous reactions have been performed with aqueous solutions of other aliphatic aldehydes and with phenylacetaldehyde (166), but the yields rapidly decrease with increasing chain length. Ketones and aromatic aldehydes do not react, but ethyl mesoxalate gives the expected product, $(COOC_2H_5)_2C(OH)CH_2COOC_2H_5$, in 33% yield.

Alkynyl ethers and some of the lower ethoxyethynylcarbinols can also be converted into hydroxy esters with aqueous formaldehyde (166).

$$(CH_3)_2C(OH)C{\equiv}COC_2H_5 + CH_2O + H_2O \xrightarrow[65\ hr.]{room\ temp.}$$

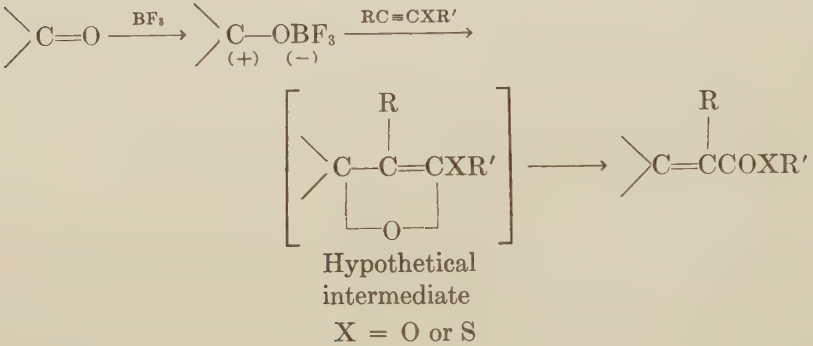
$$(CH_3)_2C(OH)CH(CH_2OH)COOC_2H_5$$

Ethynyl thioethers and carbinols derived therefrom do not react with aldehydes under these conditions (37). This is in accordance with the weak electron-donating properties of the SR group. The

ethynyl β-carbon atom cannot become sufficiently negative to add the (rather weakly electrophilic) aldehyde.

However, by increasing the positive character of the carbonyl carbon atom through coordination of the oxygen atom with boron fluoride, a variety of carbonyl compounds (even esters and amides) can be added smoothly to the β-carbon atom of ethynyl and alkynyl ethers and thioethers under *anhydrous* conditions (180,197). The products are then α,β-unsaturated esters (or thioesters).

These recent findings have not yet been fully explored, but the results obtained so far indicate that the method is of wide applicability.



In the case of aldehydes, magnesium bromide is also catalytically active, but its use is not advantageous.

On the basis of these results we can understand why *secondary* ethoxyethynylcarbinols, $RCH(OH)C{\equiv}COC_2H_5$, cannot be prepared from aldehydes and ethoxyethynylmagnesium bromide but must be obtained from ethoxyethynyl*lithium* (see Section III-C-1). The Grignard solution always contains magnesium bromide, and this catalyzes the reaction of the initially formed carbinolate, $RCH(OMgBr)C{\equiv}COC_2H_5$, with a second molecule of aldehyde.

$$RCH(OMgBr)C{\equiv}COC_2H_5 + RCHO\cdots MgBr_2 \xrightarrow{\text{2 steps}} RCH(OH)\underset{\underset{CHR}{\|}}{C}COOC_2H_5$$

R = alkyl or aryl (XII)

Magnesium bromide does not catalyze the addition of ketones (180), and therefore no complications are encountered during the preparation of *tertiary* ethoxyethynylcarbinols from ethoxyethynylmagnesium bromide.

Mixed products of type XII can be prepared from aliphatic or aromatic ethoxyethynylcarbinols by conversion into magnesium bromide salts by means of ethylmagnesium bromide, followed by treatment of the resulting solution with an aromatic aldehyde (84).

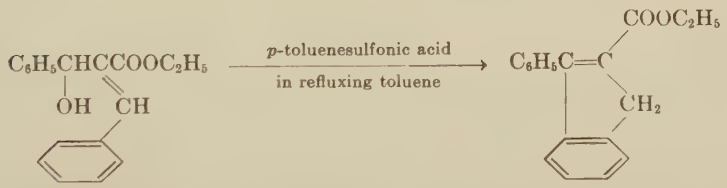
$$RCHO + LiC{\equiv}COC_2H_5 \longrightarrow RCH(OLi)C{\equiv}COC_2H_5 \xrightarrow{H_2O}$$

$$RCH(OH)C{\equiv}COC_2H_5 \xrightarrow{C_2H_5MgBr}$$

$$RCH(CMgBr)C{\equiv}COC_2H_5 \xrightarrow[\text{then } H_2O + \text{acid}]{ArCHO} RCH(OH)C(ArCH){=}COOC_2H_5$$

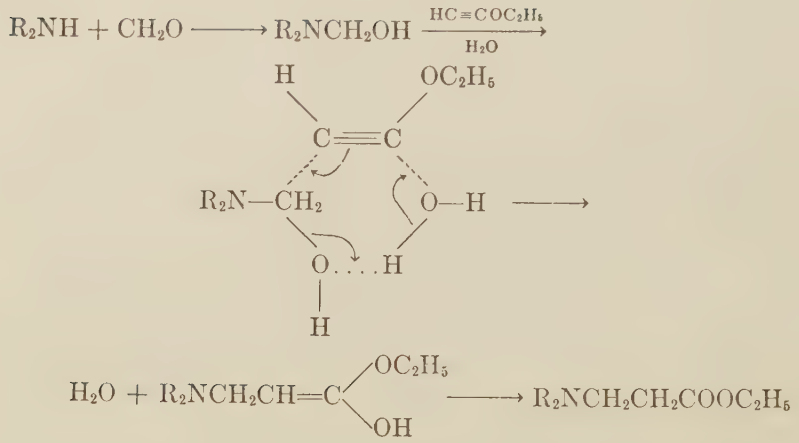
R = alkyl or aryl

It may be mentioned *inter alia* that some of the products of type XII derived from aromatic aldehydes have been converted into indenes by means of *p*-toluenesulfonic acid in refluxing toluene (84).

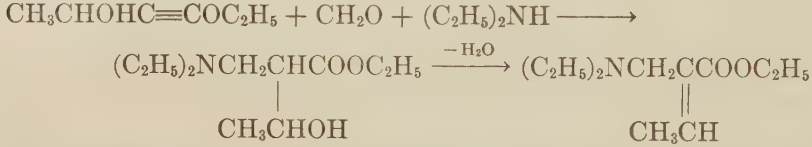


This possibly constitutes a general route to substituted indenes.

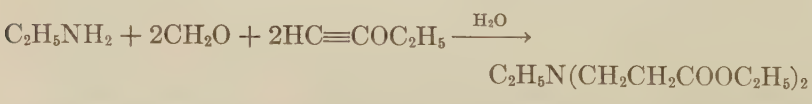
If the reaction of ethoxyethyne with formaldehyde and water is carried out in the presence of primary or secondary aliphatic amines in neutral solution, the product is a β-amino ester rather than a β-hydroxy ester (133). Probably a methylolamine is first formed from formaldehyde and the amine, which then (in hydrated form) reacts with ethoxyethyne.



Ethoxyethynylcarbinols react similarly (132).

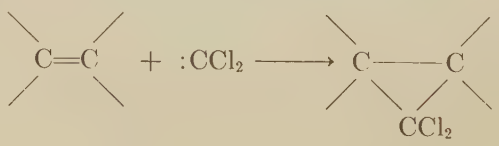


Ethoxyethyne, aqueous formaldehyde, and a *primary* amine yield a bisadduct (37).



Analogous reactions with ethynyl thioethers remain to be investigated: note, however, that (ethylthio)ethyne gives a Mannich reaction (cf. Section III-B-5).

8. Addition of Dichlorocarbene. Generally substances containing a C=C bond react with dichlorocarbene, an unstable intermediate which can be generated in the reaction mixture, among others, by the interaction of potassium *tert*-butoxide and chloroform. Cyclopropane derivatives are formed:



The literature contains no report concerning the successful interaction of ethynes with dichlorocarbene or other carbenes. However, alkoxyalkynes, RC≡COR′ (with R = H or alkyl), readily react at −20° with chloroform in the presence of potassium *tert*-butoxide. No cyclopropene derivatives have been detected in the mixture of reaction products. Probably dichlorocarbene in these cases acts as an electrophilic reagent; the primary adduct adds *tert*-butanol which is present in the mixture. Among others, a mixed acetal is formed, hydrolysis of which yields a β,β-dichloro α,β-unsaturated aldehyde (194).

$$RC{\equiv}COR' + :CCl_2 \longrightarrow \underset{(-)}{CCl_2}\underset{(+)}{CR{=}COR'} \longrightarrow$$

$$CCl_2{=}CRCH(OR')(O\cdot tert\text{-}Bu) \xrightarrow[H^+]{H_2O} CCl_2{=}CRCHO$$

E. ADDITIONS OF NUCLEOPHILIC REAGENTS TO THE TRIPLE BOND

The ethynyl thioethers differ greatly from the corresponding oxygen ethers with respect to their behavior toward *nucleophilic* reagents; therefore these groups are treated separately. As already explained in Section III-A, the oxygen ethers add nucleophilic reagents to the α-carbon atom, whereas the thioethers react at the β-carbon atom.

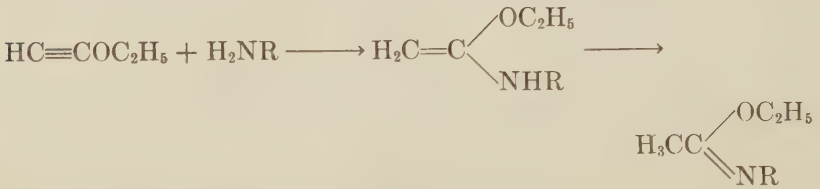
1. Reactions of Alkoxyalkynes with Amines. The strongly basic primary and secondary aliphatic amines and also piperidine readily react with ethoxyethyne. The constitution of the end product depends on the type of amine used (primary or secondary), on its quantity, and on the presence or absence of water.

The simplest case is encountered with anhydrous secondary amines; equimolar amounts of the reactants yield (α-alkoxyvinyl)dialkylamines (135).

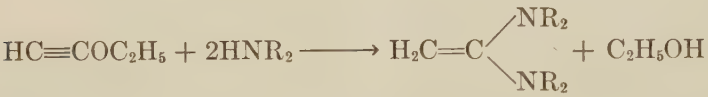
$$HC{\equiv}COC_2H_5 + HNR_2 \longrightarrow H_2C{=}C(OC_2H_5)(NR_2)$$

The same products were obtained earlier by McElvain and co-workers from keteneacetal and amines (128a).

If anhydrous primary amines are used, the initial products tautomerize to imino ethers (135).



These reactions can be followed by others if the amines are employed in excess. In such cases, replacement of the OC_2H_5 group may occur (135).



R = alkyl

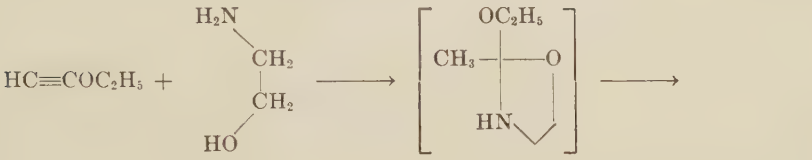
R = alkyl or aryl

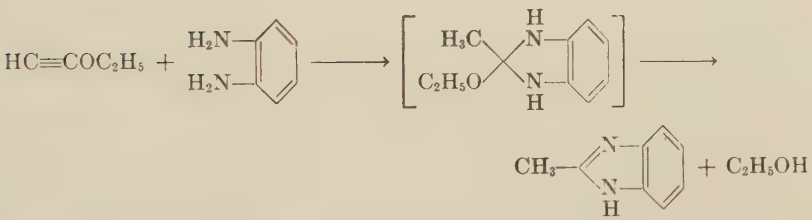
Essentially similar results have been obtained by McElvain and co-workers during reactions of keteneacetal with amines (128a).

In case the reactions require prolonged refluxing, the acetyl derivatives of the amines are also formed (37). The evolution of ethene (cf. Section III-H-2) has been proved for the reactions of 1-ethoxy-1-heptyne and 1-ethoxy-1-butyne with aniline or sodamide above 100° (29).

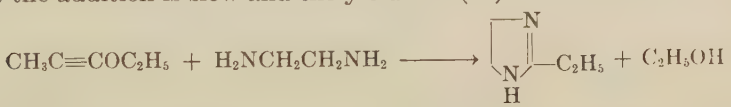
R = aryl or H

Bifunctional nucleophilic reagents with at least one active nucleophilic group, such as diamines, amino alcohols and amino thiols, easily yield heterocyclic addition products when warmed with ethoxyethyne. The yields are moderate (136).

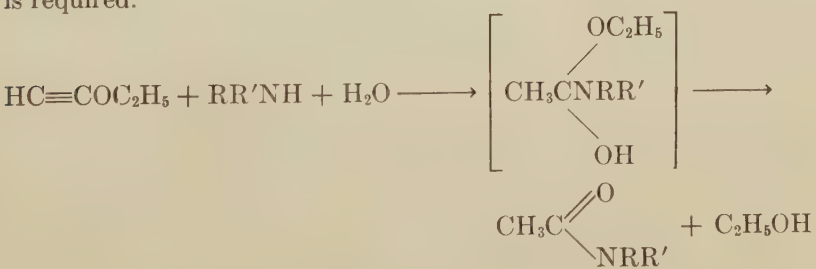




Ethoxypropyne and ethylenediamine also form a cyclized product, but the addition is slow and the yield low (30).



The addition of amines in the presence of water yields N-substituted acetamides (137). The additions are exothermic at room temperature when strongly basic amines are used. Otherwise prolonged stirring is required.



R and R′ = alkyl or H

Weakly basic amines such as aniline and diphenylamine do not react in this way. Aniline yields *N,N'*-diphenylacetamidine, the same product as obtained in the absence of water, whereas diphenylamine catalyzes the addition of water to ethoxyethyne with the formation of ethyl acetate (137).

It is interesting to note that even tertiary amines can be added to ethoxyethyne if water is present. Strong quaternary bases are formed which give stable crystalline salts (138). The conversions are very slow with the higher tertiary aliphatic amines, but trimethylamine and triethylamine react readily at room temperature.

$$HC{\equiv}COC_2H_5 + N(CH_3)_3 + H_2O \longrightarrow (CH_2{=}C(OC_2H_5)N(CH_3)_3)^+OH^-$$

The stability of these (α-alkoxyvinyl)amine derivatives in aqueous solution (the presence of the double bond has been proved by infrared spectroscopy (37)) is somewhat surprising but is doubtless due to the positive charge at the nitrogen atom.

Analogous quaternary bases have been obtained by Reppe from ethyne itself (139).

$$HC{\equiv}CH + N(CH_3)_3 + H_2O \longrightarrow (H_2C{=}CHN(CH_3)_3)^+OH^-$$

2. Reaction of Ethoxyethynylcarbinols with Amines. The interaction of ethoxyethynylcarbinols with amines is rather complex. The basicity of the amine strongly influences the course of the reaction. Three main types are known (99a,99b).

1. Partial dissociation of the carbinol is caused by warming with strongly basic amines (diethylamine) in water. We have already seen that inorganic bases also promote this dissociation (Section III-C-1).

$$RR'C(OH)C{\equiv}COC_2H_5 \longrightarrow RR'C{=}O + HC{\equiv}COC_2H_5$$

Ethoxyethyne is not obtained as such because it reacts with the amines as described above to yield substituted acetamides. For the complicated reactions occurring when the carbinols are heated with triethylamine see Section III-H-1.

2. Rearrangement of the carbinol to an α,β-unsaturated ester is the main reaction observed upon refluxing an alcoholic solution with very weakly basic amines (*m*-nitroaniline, *p*-nitroaniline).* This peculiar

* In paper 99b omission of two lines at the bottom of page 1378 causes an annoying obscurity. The lines omitted are: "...reaction product arose from a side reaction of type B. Heating of ethoxyethynylcarbinols with very weak bases like nitroanilines in...."

reaction deserves more study, since it may constitute a synthetic route to pure α,β-unsaturated esters uncontaminated with β-hydroxy esters. Such mixtures usually result from rearrangement with acids in aqueous medium (cf. Section III-C-3). The steric course of this reaction must also be studied.

$$RR'C(OH)C{\equiv}COC_2H_5 \longrightarrow RR'C{=}CHCOOC_2H_5$$

3. Amides of β-hydroxy acids are formed by treatment of the carbinol with aromatic amines such as aniline, *p*-anisidine, etc. This reaction involving the OC_2H_5 group will receive more attention in Section III-H-2.

$$RR'C(OH)C{\equiv}COC_2H_5 + C_6H_5NH_2 \longrightarrow RR'C(OH)CH_2CONHC_6H_5 + C_2H_4$$

Generally reactions of these three types occur together, but, by suitable selection of amine and reaction conditions, one can be promoted.

3. Base-Catalyzed Reaction of Alkoxyalkynes with Alcohol, Ethanethiol, or Water. As already indicated in Sections III-D-1 and III-D-3, ethoxyethyne reacts with alcohols or water under basic as well as acidic conditions. The former reactions are very much slower, however, and have not been extensively studied.

Addition of alcohol in the presence of sodium ethoxide gives a moderate yield of ethyl orthoacetate (127).

$$HC{\equiv}COC_2H_5 + 2C_2H_5OH \xrightarrow{C_2H_5O^-} H_3CC(OC_2H_5)_3$$

Sodium ethanethiolate and ethoxyethyne in liquid ammonia give a mono-adduct (192).

$$HC{\equiv}COC_2H_5 + C_2H_5SNa \xrightarrow{\text{liq. } NH_3} H_2C{=}C\begin{matrix}\diagup OC_2H_5\\ \diagdown SC_2H_5\end{matrix}$$

By prolonged refluxing of ethoxyethyne with aqueous sodium hydroxide, sodium acetate and alcohol are formed (83). Similarly, 1-ethoxy-1-heptyne, when refluxed for 16 hr. with dilute potassium hydroxide, is converted into sodium heptanoate (29). Butoxyethyne is partly hydrolyzed to butyl acetate and partly polymerized by

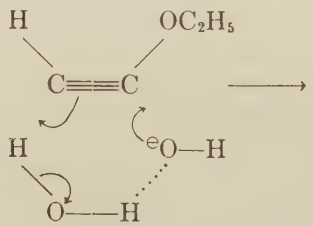
boiling with water (3). The carbinol derived from ethoxyethyne and acetaldehyde hydrates upon shaking at room temperature for 3 days with slightly alkaline water (37).

$$CH_3CH(OH)C{\equiv}COC_2H_5 + H_2O \xrightarrow{OH} CH_3CH(OH)CH_2COOC_2H_5$$

This latter reaction may constitute a general method for the preparation of β-hydroxy esters and thus be an alternative to the Reformatsky synthesis.

These base-catalyzed hydrations can be formulated as concerted reactions involving the ethynyl ether and a solvated OH^- ion.

$$HC{\equiv}COC_2H_5 + HOH\cdot OH^{(-)} \rightleftharpoons$$



$$H_2C{=}C(OC_2H_5)OH \longrightarrow CH_3COOC_2H_5$$

4. Additions of Amines and Base-Catalyzed Additions of Alcohols and Thiols to Ethynyl Thioethers. The ethynyl thioethers add amines without the aid of a catalyst (20,83,182), whereas the addition of alcohols or phenols requires the presence of a strong base (3b,42,43, 83,141,182). The addition products are invariably 1,2-disubstituted ethenes, as is shown by the formation of aldehyde 2,4-dinitrophenylhydrazones upon acid hydrolysis in the presence of 2,4-dinitrophenylhydrazine (DNPH) (20,83,140,141,182).

$$HC{\equiv}CSC_2H_5 + RNH_2 \longrightarrow RNHCH{=}CHSC_2H_5 \xrightarrow[H_2O,\ H^+]{DNPH}$$

$$DNPH{=}CHCH_2SC_2H_5$$

$$HC{\equiv}CSC_2H_5 + ROH \xrightarrow{RO^-} ROCH{=}CHSC_2H_5 \longrightarrow$$

$$DNPH{=}CHCH_2SC_2H_5$$

The enamin structure of the adducts of primary amines is corroborated by infrared spectral evidence. Bands due to NH and C=C groups are clearly present (37).

The addition product of alcohol and (ethylthio)ethyne is a mixture of the *cis* and *trans* isomers; however, these isomers easily interconvert (37) so that the primary adduct may have the *cis* configuration (resulting from *trans* addition). The configuration of the amine adducts has not been investigated.

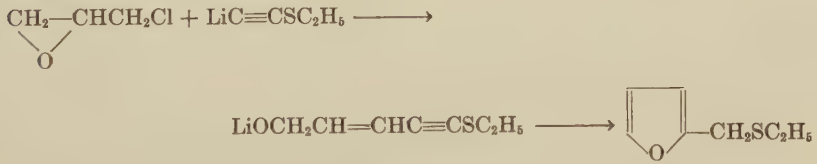
Thiolates can also be added (5,43,73,83,141).

$$HC{\equiv}CSC_2H_5 + RSNa \xrightarrow{\text{in alcohol}} RSCH{=}CHSC_2H_5$$

The product has the *cis* configuration as has been proved by measurement of the dipole moment (for R = C_2H_5: 2.25 ± 0.02 D.) (37).

It has been proved that this adduct is the primary product of the addition and not the result of a rearrangement of $CH_2{=}C(SC_2H_5)_2$. This ketenemercaptal, obtainable by treatment of ethyl orthothioacetate, $CH_3C(SC_2H_5)_3$, with traces of acids, does not rearrange to $C_2H_5SCH{=}CHSC_2H_5$ under the conditions used for the above addition (141).

A ring closure caused by nucleophilic addition to a $-C{\equiv}CSC_2H_5$ group has been observed during the reaction of epichlorohydrin with (ethylthio)ethynyllithium. Two products are obtained, the second being formed from the first; prolonged reaction times increase the proportion of the second one (178).



Nucleophilic additions of amines or alcohols to (ethylthio)ethynylcarbinols could not be performed. Strong bases like sodium ethoxide cause dissociation of the carbinols into carbonyl compound and (ethylthio)ethyne (which reacts with alcohol), whereas weakly basic amines do not react (83,140).

An explanation for the different orientation of nucleophilic additions to ethynyl oxygen and ethynyl thioethers has already been presented in Section III-A (83,140).

F. FREE RADICAL ADDITIONS TO THE TRIPLE BOND

1. Addition of Thiols. The ionic addition of thiolates has been discussed in Sections III-E-3 and III-E-4. The free thiols react faster by a free radical mechanism (20,140,142,182).

The free radical additions invariably result in attachment of the SR group to the β-carbon atom of both the ethers and the thioethers (refluxing is necessary for R = CH_3).

$$RC{\equiv}COC_2H_5 + C_2H_5S\cdot \longrightarrow C_2H_5SCR{=}\dot{C}OC_2H_5$$
$$R = H \text{ or } CH_3$$

$$C_2H_5SCR{=}\dot{C}OC_2H_5 + C_2H_5SH \longrightarrow C_2H_5SCR{=}CHOC_2H_5 + C_2H_5S\cdot$$

Likewise:

$$HC{\equiv}CSC_2H_5 + C_2H_5SH \longrightarrow C_2H_5SCH{=}CHSC_2H_5$$

Ethaneselenol also adds in this manner (83,140).

$$C_2H_5SeH + HC{\equiv}CS(\text{or O})C_2H_5 \longrightarrow C_2H_5SeCH{=}CHS(\text{or O})C_2H_5 \xrightarrow[H^+]{H_2O} C_2H_5SeCH_2CHO$$

If an excess of ethanethiol is used with ethoxyethyne, a second mole is added (142).

$$C_2H_5SCH{=}CHOC_2H_5 + C_2H_5SH \longrightarrow C_2H_5SCH_2CH(OC_2H_5)(SC_2H_5)$$

A third mole of thiol reacts only if a small amount of sulfuric acid is subsequently added.

$$C_2H_5SCH_2CH(OC_2H_5)(SC_2H_5) + C_2H_5SH \xrightarrow{H^+} C_2H_5SCH_2CH(SC_2H_5)_2 + C_2H_5OH$$

The monoadduct $C_2H_5OCH{=}CHSC_2H_5$ of ethanethiol to ethoxyethyne initially has the *cis* structure (*trans* addition), but during distillation it partly isomerizes to the *trans* isomer (142,192).

The monoadduct of ethanethiol (and by analogy probably also those of the other thiols) to (alkyl (or aryl)thio)ethynes likewise has the *cis* configuration. Di-adducts are only obtained with the aid of an acid catalyst (83,141). This is an equilibrium reaction (141).

$$C_2H_5SCH{=}CHSC_2H_5 + C_2H_5SH \rightleftharpoons C_2H_5SCH_2CH(SC_2H_5)_2$$

For additions of thiols to ethoxyethynyl- and (ethylthio)ethynylcarbinols, the use of di-*tert*-butyl peroxide as initiator is necessary (142–144). Satisfactory yields are obtained.

$$RR'C(OH)C{\equiv}COC_2H_5 + C_2H_5SH \longrightarrow RR'C(OH)\underset{\displaystyle SC_2H_5}{\underset{|}{C}}{=}CHOC_2H_5$$

(XIII)

The configurations of the products XIII have not been determined.

It is interesting to note that these substances are so easily rearranged into unsaturated aldehydes (XIV) (143) by traces of acids that they can be distilled only from flasks previously washed with alkali; otherwise the distillates consist of the rearranged products XIV.

$$RR'C(OH)\underset{\displaystyle SC_2H_5}{\underset{|}{C}}{=}CHOC_2H_5 \xrightarrow{H^+} RR'C{=}\underset{\displaystyle SC_2H_5}{\underset{|}{C}}CHO + C_2H_5OH$$

(XIII) (XIV)

The same aldehydes, XIV, are obtained by thiol addition to (ethylthio)ethynylcarbinols and subsequent treatment with acid (83,140; cf. also 20).

$$RR'C(OH)C{\equiv}CSC_2H_5 + C_2H_5SH \xrightarrow[\text{refluxing dioxane}]{\text{di-}tert\text{-butyl peroxide}}$$

$$RR'C(OH)\underset{\displaystyle SC_2H_5}{\underset{|}{C}}{=}CHSC_2H_5 \xrightarrow[H^+]{H_2O} RR'C{=}\underset{\displaystyle SC_2H_5}{\underset{|}{C}}C\begin{matrix}H\\ \diagup\\ \diagdown\\ O\end{matrix}$$

(XIV)

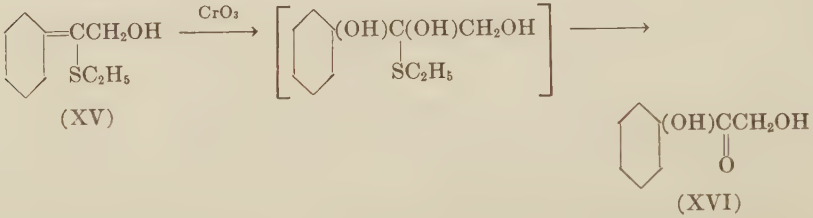
(isolated as 2,4-dinitrophenylhydrazone)

The thioenol ether groups of the rearranged products XIV are very resistant to hydrolysis (143). Conversion into ketols can be effected, however, when the aldehyde carbonyl is reduced with lithium aluminum hydride (144).

$$RR'C{=}CCHO \xrightarrow{LiAlH_4} RR'C{=}CCH_2OH \xrightarrow[H_2O]{HgCl_2} RR'CHCCH_2OH$$

(XIV)

The α,α'-dihydroxy ketone (XVI) has been obtained by hydroxylation of the double bond in the unsaturated alcohol (XV), followed by hydrolysis (144).



(XV) (XVI)

These conversions may be useful for syntheses in the steroid series.

2. Addition of Thio Acids. The addition of thio acids to (ethylthio)-ethyne proceeds readily at room temperature in ether and gives a β-adduct (20). (Addition of thio acids to ethoxyethyne has not yet been studied.)

$$RCOSH + HC{\equiv}CSC_2H_5 \longrightarrow RCOSCH{=}CHSC_2H_5$$

$$R = CH_3,\ C_2H_5,\ \text{or}\ C_6H_5$$

Hydrolysis of the products with R = CH_3 or C_2H_5 yields primarily (ethylthio)acetaldehyde, whereas, curiously, the product with R = C_6H_5 gives (benzoylthio)acetaldehyde (20,140).

$$RCOSCH{=}CHSC_2H_5 \xrightarrow[H^+]{H_2O} OHCCH_2SC_2H_5$$

$$R = \text{alkyl}$$

$$C_6H_5COSCH{=}CHSC_2H_5 \xrightarrow[H^+]{H_2O} C_6H_5COSCH_2CHO$$

Thiobenzoic acid in the presence of di-*tert*-butyl peroxide has been added to the (ethylthio)ethynylcarbinol derived from acetone in a rather low yield (20,140).

$$(CH_3)_2C(OH)C{\equiv}CSC_2H_5 + C_6H_5COSH \longrightarrow$$

$$(CH_3)_2C(OH)C{=}CHSC_2H_5 \xrightarrow[H^+]{H_2O} (CH_3)_2C{=}CCHO$$

$$SCOC_6H_5 \qquad\qquad SCOC_6H_5$$

The reaction between thiobenzoic acid and the corresponding ethoxyethynylcarbinol proceeds differently; the much greater basicity of the ethoxyethynyl compound leads to an ionic addition of the acid (143).

$$(CH_3)_2C(OH)C{\equiv}COC_2H_5 + C_6H_5COSH \longrightarrow$$
$$(CH_3)_2C(OH)CH{=}C(OC_2H_5)SCOC_6H_5 \xrightarrow[H^+]{H_2O}$$
$$(CH_3)_2C{=}CHCOOC_2H_5 + C_6H_5COSH$$

G. MISCELLANEOUS REACTIONS OF THE TRIPLE BOND

There are a number of reactions involving the triple bond of ethynyl ethers which cannot be classified unequivocally as electrophilic, nucleophilic, or free radical additions. These comprise some additions, ring closures, and polymerizations.

1. Reduction. Mention has already been made in several sections of partial catalytic reductions of the triple bond of ethynyl ethers. The hydrogenations practically stop at the intermediate vinyl ether stage if a special catalyst like the Lindlar palladium catalyst (109) or palladium on calcium carbonate in pyridine is used (cf. Section III-C-5). By using an unpoisoned palladium, platinum, or nickel catalyst, the hydrogenation may proceed to completion, often without perceptible change of rate after passing the vinyl ether stage. Saturated ethers are then formed (3,13,32). Thus, 1-phenyl-2-methoxyethyne has been reduced to the saturated ether with platinum or palladium catalysts. Some methanol and ethylbenzene were also formed (32), but this hydrogenolysis of the ether bond did not take place with Raney nickel.

Perhydrogenation of ethoxyethynylcarbinols may be a convenient method for the preparation of γ-hydroxy ethers.

$$RR'C(OH)C{\equiv}COC_2H_5 \longrightarrow RR'\underset{\displaystyle OH}{\underset{|}{C}}CH_2CH_2OC_2H_5$$

Partial catalytic or chemical reduction of ethoxyethynylcarbinols has been treated in Section III-C-5.

Ethoxyethyne is reduced to ethyl vinyl ether by an ethereal solution of lithium aluminum hydride at room temperature (37). This result is an exception to the general rule that this reagent only reduces an ethyne bond adjacent to a hydroxyl group.

2. Addition of Halogens. Occasional attention has been paid to the addition of halogens to ethynyl ethers and thioethers. Jacobs, Cramer, and Weiss (21) prepared the dibromide and diiodide of phenoxyethyne by treatment of this ether with the appropriate halogen in carbon tetrachloride solution.

$$HC{\equiv}COC_6H_5 \xrightarrow[CCl_4]{X_2} CHX{=}CX(OC_6H_5)$$

X = Br or I

Jacobs and Whitcher (41) obtained 1-phenoxy-1,2,2-triiodoethene during attempts to prepare 1-iodo-2-phenoxyethyne from metallic derivatives of phenoxyethyne and iodine. The analogous tribromo derivative was formed from 1-bromo-2-phenoxyethyne and bromine in carbon tetrachloride.

$$BrMgC{\equiv}COC_6H_5 \xrightarrow{I_2} IC{\equiv}COC_6H_5 \xrightarrow{I_2} I_2C{=}CIOC_6H_5$$

Dibromides have also been obtained by Fromm and co-workers (7,71) from bis(arylthio)ethynes and bromine in chloroform. They report that the dibromides cannot be brominated further.

$$ArSC{\equiv}CSAr \xrightarrow[CHCl_3]{Br_2} ArSCBr{=}C(Br)SAr$$

Baganz and Triebsch (70) obtained a dichloride as well as a tetrachloride from 1,2-bis(ethylthio)ethyne.

3. Reactions with Trichloroacetic Anhydride and Trichloroacetyl Chloride. Trichloroacetic anhydride reacts very readily with ethoxyethyne in ether (122).

$$CCl_3COOH + HC{\equiv}COC_2H_5 \longrightarrow H_2C{=}C\begin{matrix}OC_2H_5\\ \diagdown\\ \diagup\\ OCOCCl_3\end{matrix} \xrightarrow{CCl_3COOH} CH_3COOC_2H_5 + (CCl_3CO)_2O$$

$$(CCl_3CO)_2O + HC{\equiv}COC_2H_5 \longrightarrow CCl_3CCH{=}C\begin{matrix}OC_2H_5\\ \diagdown\\ \diagup\\ OCOCCl_3\end{matrix} \xrightarrow{C_2H_5OH}$$

$$\begin{matrix}CCl_3CCH{=}C\begin{matrix}OC_2H_5\\ \diagdown\\ \diagup\\ OCOCCl_3\end{matrix}\\ \|\\ O\end{matrix}$$

(XVII)

$$CCl_3COCH_2COOC_2H_5 + CCl_3COOC_2H_5$$

(XVIII)

The substance (XVII) formed can also be obtained in good yield by slowly adding ethoxyethyne to cold trichloroacetic acid, because these compounds then first react to yield the anhydride (cf. Section III-D-4). The structure of XVII is proved by conversion into ethyl trichloroacetoacetate (XVIII).

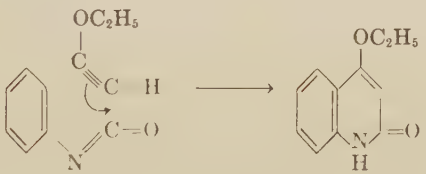
Essentially the same type of addition can be effected between trichloroacetyl chloride and ethoxyethyne (122).

$$CCl_3COCl + HC{\equiv}COC_2H_5 \longrightarrow CCl_3COCH{=}C\begin{matrix}OC_2H_5\\Cl\end{matrix} \xrightarrow{C_2H_5OH} CCl_3COCH_2COOC_2H_5 + C_2H_5Cl$$

Probably other highly halogenated acid anhydrides and chlorides like trifluoroacetic anhydride, dichloroacetic anhydride, etc., would also react spontaneously. Acetic anhydride requires the assistance of boron fluoride and gives a moderate yield (181).

The behavior of alkynyl thioethers toward anhydrides has not yet been studied.

4. Reactions with Aryl Isocyanates. The reaction of phenyl isocyanate, preferably diluted with nitromethane, with ethoxyethyne at room temperature results in the gradual deposition of crystalline 4-ethoxy-2-quinolone (69,173).



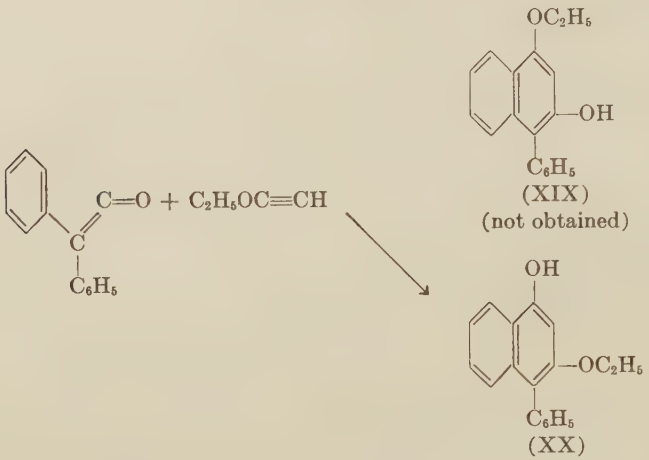
42% yield after 6 weeks

Even after several weeks the conversion is still incomplete. Higher temperatures are unfavorable because brown oils are then formed. In weakly polar solvents very low yields are obtained. The reaction has also been performed with *p*-tolyl isocyanate, α-naphthyl isocyanate, and *p*-nitrophenyl isocyanate (37,69,173).

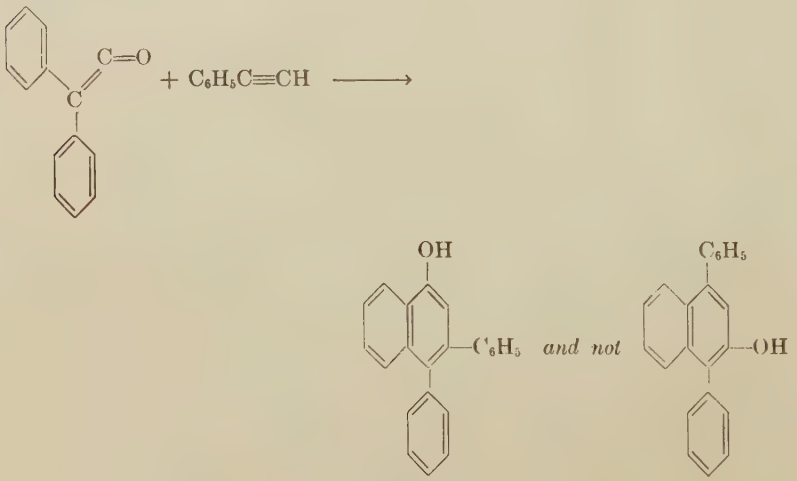
5. Reactions with Diphenylketene. Diphenylketene has been subjected to reaction with ethoxyethyne in different solvents. The solvent has a strong influence on the nature of the resulting product.

In benzene at room temperature, 1-phenyl-2-ethoxy-4-hydroxynaphthalene (XX) is obtained together with considerable amounts

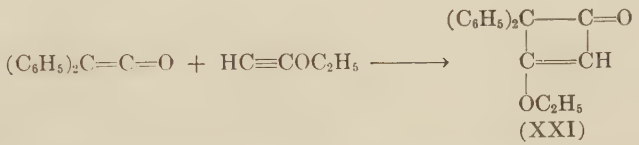
of brown oils (124,173). By analogy with the above-mentioned reaction with phenyl isocyanate, the isomeric 1-phenyl-2-hydroxy-4-ethoxynaphthalene (XIX) might have been expected. That isomer XX was in fact formed has been established both by degradation and by synthesis (124,173).



The rather peculiar ring closure to XX is similar to the one found by Smith and Hoehn (134) during the reaction of diphenylketene with phenylethyne.

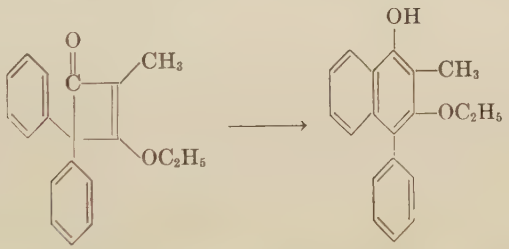


If the reaction of diphenylketene with ethoxyethyne is performed in petroleum ether at −30°C., another compound, possibly the cyclobutenone ether (XXI), is obtained, which can be converted into the naphthol (XX) by warming in benzene (37). In nitromethane at −20°C. a third adduct is formed, which was originally regarded as being XXI (124). Recent investigations have cast doubts on this structure, however (37); a new formula has not yet been proposed. This compound does not isomerize into the naphthol (XX) by heating.



(XXI)

Ethoxy- or methoxypropyne and diphenylketene similarly yield cyclobutenone ethers, which can be transformed into naphthols by gentle heating (124).



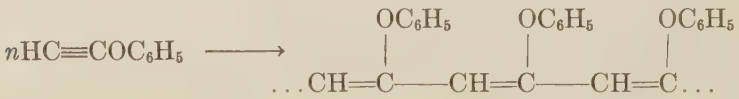
6. Polymerizations. Polymerizations of phenoxy- and ethoxyethyne and also of 1-phenyl-2-methoxyethyne have been studied by Jacobs and co-workers (32,40,150).

Phenoxyethyne polymerizes spontaneously at a moderate rate at room temperature (40). A deep red liquid is formed, which turns gradually to a hard, brittle, black solid. Ionic and free radical catalysts or inhibitors have a negligible effect on the polymerization rate; only cadmium iodide has some effect. The first formed, low molecular weight polymers, isolated by precipitation, seem to have a polyene structure, as evidenced by their ultraviolet absorption spectra and the color reactions which they give with strong acids and salts like antimony trichloride. They are thermosetting. The later, almost insoluble polymers appear to be crosslinked and less

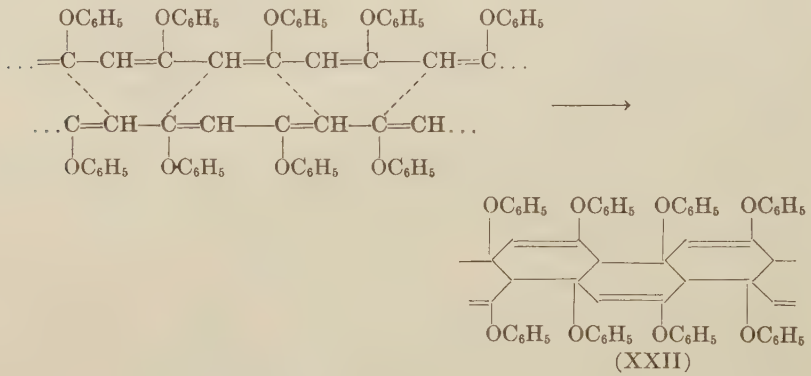
conjugated. They lose phenol by heating (up to 46% of the phenoxyl content can be lost).

The polymerization has been formulated as follows (40):

First stage: formation of conjugated polymer.

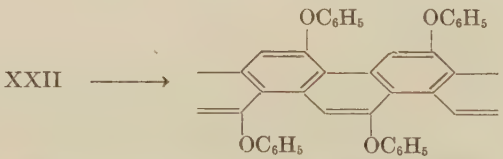


Second stage: crosslinking.



(XXII)

Third stage: elimination of phenol by heating.



1-Phenyl-2-methoxyethyne also polymerizes very readily (32). At room temperature about a week is required for complete conversion. On distillation, even at 58°/1 mm., 5–10% of the ether polymerizes to a clear orange glass. Inhibitors are without effect.

From the polymer two crystalline materials, a dimer (m.p. 134–135°) and a trimer (m.p. 165–166°), have been isolated. Their structures have not been determined.

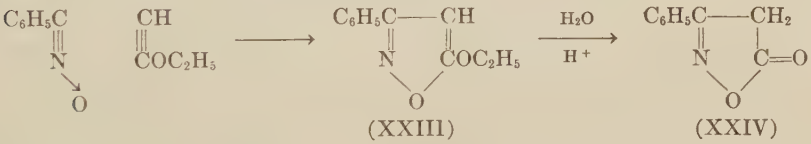
Ethoxyethyne undergoes a complicated, step-wise polymerization at room temperature and above. The first step is the reversible formation of 1,3-diethoxybut-3-en-1-yne (150).

$$2HC{\equiv}COC_2H_5 \rightleftharpoons H_2C{=}C(OC_2H_5){-}C{\equiv}COC_2H_5$$

Another product formed is a tetramer minus C_4H_8 ($= 2C_2H_4$ or $= +2H_2O - 2C_2H_5OH$). Ethene indeed is produced (together with a very little ethyne) at 60° during long reaction periods, but under the conditions most favorable for isolating the "tetramer" (100 hr. at 40°) ethanol is found. Traces of moisture seem to favor the formation of the "tetramer." At later stages of the polymerization a complex mixture and finally an insoluble, hard, black, infusible glass with the approximate composition $(C_2H)_x$ are formed.

Phenoxyethyne polymerizes about ten times more rapidly than ethoxyethyne (at 40°).

7. Reaction of Ethoxyethyne with Nitrile Oxides. Refluxing of an ethereal solution of an aromatic nitrile oxide with ethoxyethyne gives a good yield of 3-aryl-5-ethoxyisoxazole (XXIII) (188), which by acid hydrolysis can be converted into the corresponding 3-aryl-5-isoxazolone (XXIV).



(XXIII) (XXIV)

H. REACTIONS INVOLVING THE ETHER GROUP OF ETHYNYL ETHERS

1. Formation of Cyclobutenone Ethers. Ficini (29) observed that ethoxyheptyne by heating at 120° evolves ethene and—in excellent yield—forms a product which is a dimer minus C_2H_4. Hydrolysis gives dihexyl ketone. Further study of the product by Nieuwenhuis

$$2RC{\equiv}COC_2H_5 \longrightarrow \underset{\displaystyle C_2H_5OC=\!=\!=CR}{\overset{\displaystyle RCH-\!-C=O}{|\quad\quad|}} \xrightarrow{KOH}$$

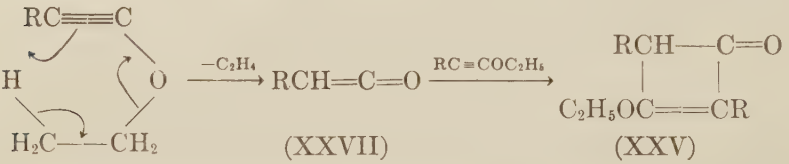
(XXV)

$$\underset{\displaystyle O=C-\!-\!-CHR}{\overset{\displaystyle RCH-\!-C=O}{|\quad\quad|}} \xrightarrow{H_2O} RCH_2COCH_2R + CO_2$$

(XXVI)

and Arens revealed that it is a cyclobutenone ether (XXV) (87,173). Alkaline hydrolysis of this compound at first gives rise to a cyclobutanedione (XXVI), which by boiling with acid is converted into a symmetrical ketone and carbon dioxide (cf. also 145–147).

Very probably the pyrolysis of the ether first yields an aldoketene (XXVII), which immediately reacts with a second mole of the alkynyl ether to form the cyclobutenone ether (XXV) (cf. Section III-G-5).



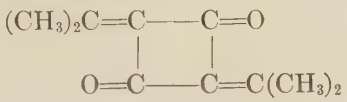
This view is supported by a preliminary investigation on the kinetics of the ethene formation, which showed that this indeed is a unimolecular reaction (185), and also by the fact that pyrolysis in the presence of aniline gives an anilide in almost quantitative yield. Futhermore, the rate of ethene formation is hardly influenced by the presence of aniline; the amount of ethene formed is approximately twice as large as in the absence of aniline because now each mole of alkynyl ether gives a mole of ethene.

$$RC{\equiv}COC_2H_5 \longrightarrow RCH{=}C{=}O \xrightarrow{C_6H_5NH_2} RCH_2CONHC_6H_5$$

In the presence of aniline there is a competition between aniline and unchanged acetylenic ether for the ketene; the preferential formation of anilide shows that the rate of the anil formation is much faster than the rate of cyclobutenone ether formation. Thus, it must be possible to use alkynyl ethers as potential aldoketenes. This is important because aldoketenes, as such, are difficult to handle. Applications are mentioned in Sections III-H-2 and III-H-3.

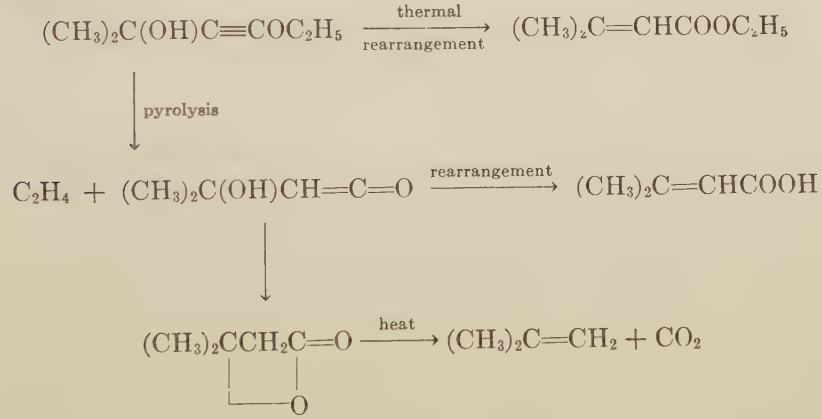
The elimination of alkene by pyrolysis of alkynyl ethers is a general reaction. Methyl ethers, of course, are not split, but the higher ethers, including those with branched alkoxy groups, readily eliminate alkene and give rise to cyclobutenone ethers when heated (187). The various ethers differ somewhat with respect to the ease of alkene formation, but a detailed investigation of the reaction rates has not been performed. The pyrolysis of ethoxyethyne has not been studied because this compound polymerizes easily (cf. Section III-G-6).

Heating of the carbinol $(CH_3)_2C(OH)C{\equiv}COC_2H_5$ in benzene yields, among other products, a small amount of 1,3-bisisopropylidenecyclobutane-2,4-dione (XXVIII) (174), which may be a dehydrated



(XXVIII)

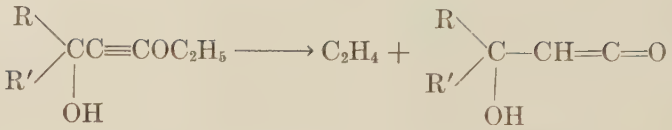
dimer of the hydroxy ketene $(CH_3)_2C(OH)CH{=}C{=}O$. The same carbinol, when heated in triethylamine, gives a gas consisting of ethene, isobutene, and carbon dioxide, whereas the liquid product contains, among others, dimethylacrylic acid and its ethyl ester. The formation of these compounds can be explained as follows:



The thermal decomposition of β-isovalerolactone into isobutene and carbon dioxide is known (191).

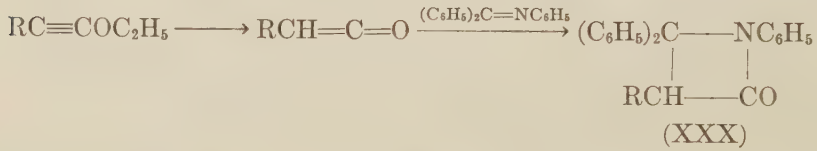
The explosions sometimes observed during incautious distillations of ethoxyethynylcarbinols (cf. Section II-B) are doubtless due to such gas-producing decompositions.

2. Formation of Amides. It has already been mentioned in the preceding section that ethoxyalkynes, when heated with aniline, give anilides in high yield (29). The same applies to ethoxyethynylcarbinols (99a,99b), which yield anilides of β-hydroxy acids (cf. Section III-E-2). The latter fact indicates that the unknown hydroxy ketenes (XXIX) may exist during a short time.



(XXIX)

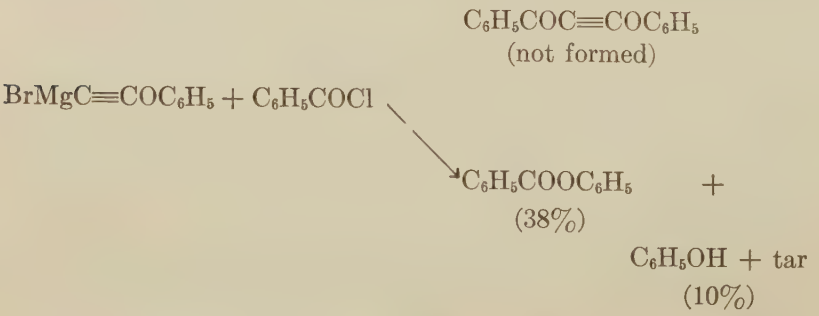
3. Formation of β-Lactams from Aromatic Imines. When ethoxyalkynes are slowly added to a refluxing solution of an aromatic imine such as benzophenone anil in xylene, satisfactory yields of β-lactams (XXX) are obtained (186).



(XXX)

The yields decrease considerably when the ethoxyalkyne is added at once to the imine solution because the unchanged ethoxyalkyne competes with the imine for the intermediate ketene, and cyclobutenone ethers are formed as by-products (cf. Section III-H-1).

4. Elimination of the C_6H_5O Residue from Phenoxyethyne. The reaction of metallic derivatives of phenoxyethyne ($NaC{\equiv}COC_6H_5$ and $BrMgC{\equiv}COC_6H_5$) with acid chlorides or anhydrides in ether, even at −15°, does not yield the expected phenoxyethynyl ketones; phenol esters, together with phenol and much tarry material, are formed (21).



The iodomagnesium derivative heated alone in dibutyl ether at 90–105° gives a clear yellow solution from which phenol can be isolated in 86% yield (21).

I. REACTIONS INVOLVING THE THIOETHER GROUP OF ETHYNYL THIOETHERS

The triple bond in ethynyl thioethers and ethynylene bisthioethers is not readily attacked by organic peracids, and therefore these reagents can be used for the preparation of sulfones (see Tables IV and VI).

No sulfones of the type $HC{\equiv}CSO_2R$ are recorded in the literature; the compound with R = *tert*-butyl has been obtained in pure condition in this laboratory by oxidation of *tert*-butylthioethyne at 0° with a mixture of acetic acid, acetic anhydride, and hydrogen peroxide (37).

Backer and Strating (8,149) have studied the reactions of 1,2-bis-(*tert*-butylsulfonyl)ethyne with alcohols, thiols, and amines. With alcohols and thiols, monoadducts are formed which are apparently mixtures of *cis* and *trans* isomers. For the addition of phenol it is advantageous to use some sodium phenoxide as catalyst.

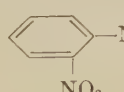
$$tert\text{-}C_4H_9SO_2C{\equiv}CSO_2\cdot tert\text{-}C_4H_9 + ROH \longrightarrow tert\text{-}C_4H_9SO_2C(OR){=}CHSO_2\cdot tert\text{-}C_4H_9$$

The reactions with amines also initially give monoadducts, but complications arise from the fact that an excess of amine sometimes causes nucleophilic substitution of a sulfonyl group which is eliminated as *tert*-butylsulfinic acid.

$$RSO_2C{\equiv}CSO_2R \xrightarrow{R'NH_2} RSO_2C(NHR'){=}CHSO_2R \xrightarrow{R'NH_2} (R'NH)_2C{=}CHSO_2R + RSO_2H$$

R = *tert*-C_4H_9

It is interesting to note that a substance with the presumed structure XXXI has been obtained as a by-product from the reaction of the disulfone with *o*-nitroaniline.

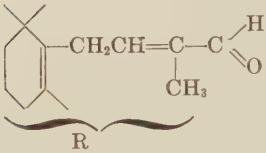


(m. p. 225°)

(XXXI)

J. SOME REAGENTS RELATED TO ETHYNYL ETHERS

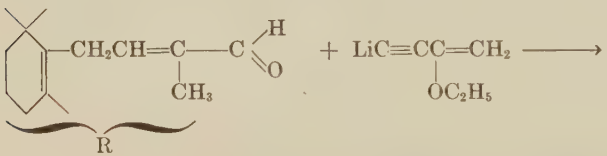
1. 1-Ethoxybut-1-en-3-yne. This substance, which can be obtained from 1,4-dichlorobut-2-yne and sodium ethoxide in refluxing alcohol (151) or directly from diacetylene by alkali-catalyzed alcohol addition (153), has been used by Inhoffen, Bohlmann, and Rummert (152) for the synthesis of unsaturated aldehydes from aldehydes or ketones containing four carbon atoms less than the products.



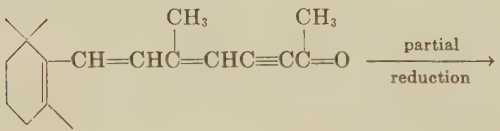
$$\text{carbinol} \xrightarrow[+\ \text{quinoline}]{H_2\ (Pd/C)} RCH(OH)CH{=}CHCH{=}CHOC_2H_5 \xrightarrow[\text{room temp.}]{\text{dil. } H_2SO_4 \text{ in alcohol}}$$

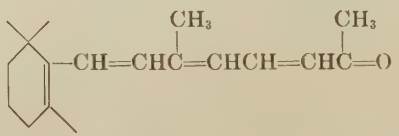
The method has also been applied to cyclohexanone (155).

2. 2-Ethoxybut-1-en-3-yne. Samokhvalov, Rubstov, Miropol'skaya, and Preobrazhenskiĭ (154) used an isomer of the former substance for the synthesis of a polyene ketone.



$$RCH(OH)C{\equiv}CC(OC_2H_5){=}CH_2 \xrightarrow[\text{in alcohol}]{1\%\ H_2SO_4}$$





"C_{18} ketone" related to vitamin A

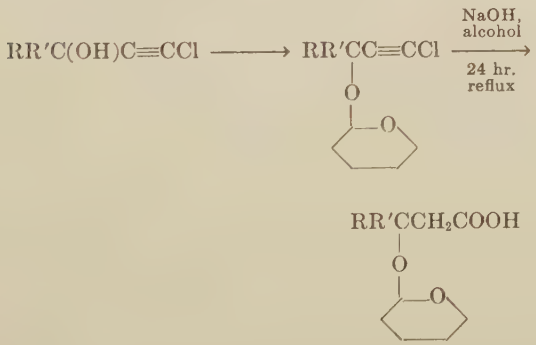
3. Chloroethynylcarbinols. Julia and Surzur (156) have developed an interesting method for the preparation of α,β-unsaturated aldehydes which is similar to the one employing ethoxyethyne (Section III-C-5). They start with carbinols derived from ethyne itself, substitute the ethynyl hydrogen atom by chlorine through the action of hypochlorite, reduce with lithium aluminum hydride, and subject the product to rearrangement.

$$\underset{\text{(XXXII)}}{RR'C(OH)C{\equiv}CH} \xrightarrow{NaOCl} RR'C(OH)C{\equiv}CCl \xrightarrow{LiAlH_4}$$

$$RR'C(OH)CH{=}CHCl \xrightarrow{H^+} RR'C{=}CHCHO$$

Satisfactory yields are achieved. A shorter route to the chloroethynylcarbinols consists of treatment of 1,2-dichloroethene with lithium amide in liquid ammonia, after which a ketone is added (189).

The chlorinated carbinols can also be transformed into α,β-unsaturated acids by first protecting the OH group with dihydropyran, then hydrolyzing the chloroethyne group by prolonged boiling with alcoholic sodium hydroxide, and subsequently splitting off the tetrahydropyranyl group and water with acid (157).



Attention is drawn to a recently published alternative method for the conversion of ethynylcarbinols like XXXII into α,β-unsaturated aldehydes (196).

$$RR'C(OH)C{\equiv}CH \xrightarrow{Ac_2O} RR'C(OAc)C{\equiv}CH \xrightarrow{AgOAc}$$

$$RR'C{=}C{=}CHOAc \xrightarrow{\text{hydrolysis}} RR'C{=}CHCHO$$

IV. Experimental

A. PREPARATION OF ETHOXYETHYNE

$$CHCl{=}CHOC_2H_5(cis) + KOH \longrightarrow HC{\equiv}COC_2H_5 + KCl + H_2O$$

Use safety glasses!

In a 500 ml. round-bottomed flask, equipped with a Vigreux column (30 cm. in length, 2 cm. in diameter) connected to a descending condenser, 150 g. of ethyl β-chlorovinyl ether (mixture of *cis* and *trans* isomers) (162) is covered with 350 g. of freshly powdered potassium hydroxide (note 1). A brown color may develop immediately. Care is taken that the liquid is well mixed with the solid. The flask is quickly heated in an oil bath. At about 120° (bath temperature) a rather vigorous reaction sets in, and ethoxyethyne distills from the mixture. The temperature at the outlet of the Vigreux column may rise some 10° above the boiling point of the ether (51°), but the reaction should not be allowed to become too vigorous. If necessary, the heating bath is temporarily removed.

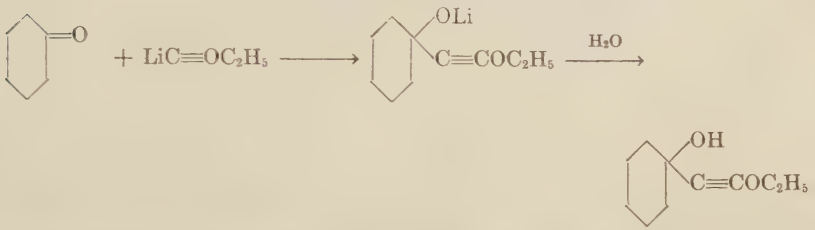
When the reaction subsides, heating at 150° is continued until no further distillate is obtained (about 0.5 hr.). To obtain optimum yields, the receiver containing the bulk of the material may be replaced by a trap cooled in a slurry of acetone and solid carbon dioxide, whereupon the remaining volatile materials can be distilled from the dark brown reaction mixture in a vacuum of about 20 mm.

The distillates are combined, dried with a little anhydrous sodium sulfate, and redistilled using a Vigreux column 15 cm. in length. The fraction boiling at 49–53° constitutes the desired substance. The yield depends upon the quality of the potassium hydroxide used and upon the *cis* content of the ethyl β-chlorovinyl ether. Usually 30–45 g. is obtained.

The residue from the distillation contains ethanol, much *trans*- and some *cis*-ethyl β-chlorovinyl ether, and chloroacetaldehyde diethylacetal.

Note 1: Potassium hydroxide should be powdered shortly before use. Commercial powder is unsatisfactory, probably because the surface of the fine grains is covered with carbonate. The usual pellets are hard to crush; a mill must be used. Technical lumps, which sometimes have a green color, can be powdered and screened easily and yield a satisfactory material. A sieve with mesh width of 0.25–0.3 mm. should be used.

B. PREPARATION OF AN ETHOXYETHYNYLCARBINOL
(1-(1′-Hydroxycyclohexyl)-2-ethoxyethyne)



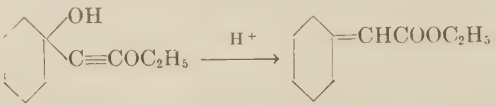
A dry three-necked 250 ml. round-bottomed flask is equipped with stirrer, dropping funnel, thermometer, gas inlet tube, and reflux condenser closed with a calcium chloride tube, the end of which is connected with a bubble counter. The air is replaced by dry nitrogen, and an ethereal solution (about 1.5*N*) containing 0.22 mole of methyllithium is then quickly added to the flask. A very slow stream of nitrogen is maintained during the whole experiment. A solution of 15.4 g. (0.22 mole) of ethoxyethyne in 20 ml. of absolute ether is added in 10 min. at room temperature. The evolution of methane ceases after about 15 min., indicating completion of the reaction. The flask is then cooled to $-20°$ in a bath of acetone and solid carbon dioxide.

Through the dropping funnel a mixture of 20 g. (0.204 mole) of freshly distilled cyclohexanone and 50 ml. of absolute ether is slowly added to the stirred milky solution at $-20°$. The addition requires about 0.5 hr. Cooling is continued for another hour; the cooling bath is then removed. After standing 1 hr. at room temperature, the mixture is stirred into 250 ml. of water; the ethereal layer is separated, twice washed with a small quantity of water, and dried with anhydrous sodium sulfate. The ether is removed by distillation at ordinary pressure (note 1). Care is taken that the residue is not overheated (bath should be kept below 60°). When most of the ether is removed, the receiver is changed and distillation is continued *in vacuo* in an atmosphere of nitrogen. *Wear safety glasses!*

The desired 1-(1′-hydroxycyclohexyl)-2-ethoxyethyne boils at 102–103°/3 mm., n_D^{20} 1.4839. The substance crystallizes when cooled in ice, m.p. 7.5–8°. The yield is 17.5–21 g. (51–61%).

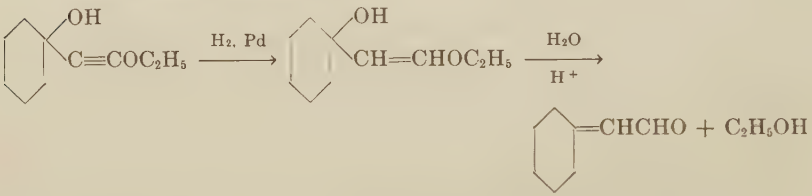
Note 1: In view of the sensitivity of the carbinol to traces of acids, it is desirable to wash the distillation apparatus with ammonia before drying.

C. REARRANGEMENT OF AN ETHOXYETHYNYLCARBINOL INTO AN α,β-UNSATURATED ESTER
(Preparation of Ethyl Cyclohexylideneacetate)



A solution of 25 g. of 1-(1′-hydroxycyclohexyl)-2-ethoxyethyne in 25 ml. of ether is shaken with 25 ml. of 0.1*N* hydrochloric acid. Heat is evolved. After 30 min. the ethereal layer is washed with cold 5% potassium carbonate solution and water, then dried with sodium sulfate and distilled. Ethyl cyclohexylidene acetate boils at 91–92°/4 mm., n_D^{20} 1.4776; yield 22.5 g.

D. PREPARATION OF AN α,β-UNSATURATED ALDEHYDE FROM AN ETHOXYETHYNYLCARBINOL
(Cyclohexylideneacetaldehyde)



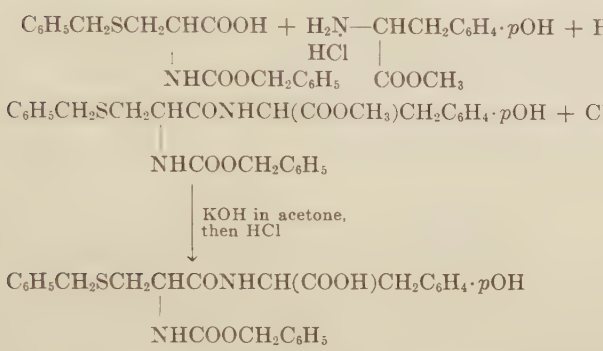
A solution of 25 g. of 1-(1′-hydroxycyclohexyl)-2-ethoxyethyne in 150 ml. of purified light petroleum, b.p. 40–60° (note 1), containing 0.5 g. of 10% palladium on carbon and 5 ml. of pyridine is shaken with hydrogen at room temperature. The hydrogenation is discontinued when 3650 ml. of hydrogen (measured above water at 760 mm. and 20°) is absorbed.

The catalyst is filtered off and the solution shaken with 50 ml. of 0.1*N* hydrochloric acid during 30 min. at room temperature.

The organic layer is then separated, twice washed with water and, after distilling off the solvent, distilled at reduced pressure in nitrogen. Cyclohexylideneacetaldehyde boils at 83–87°/16 mm., n_D^{20} 1.4880; yield 15 g.

Note: 1 Olefin-free light petroleum is prepared by shaking the commercial material, b.p. 40-60°, with concentrated sulfuric acid, washing with water and with 2*N* sodium hydroxide solution and again with water, and drying with calcium chloride. It is carefully distilled using a 20 cm. Widmer column. The fraction boiling between 40 and 50° is used.

E. PREPARATION OF A DIPEPTIDE BY MEANS OF ETHOXYETHYNE
(*N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteinyl-L-tyrosine)



A mixture of 7 g. (.020 mole) of *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteine, 4.6 g. (.020 mole) of L-tyrosine methyl ester hydrochloride, 100 ml. of ethyl acetate (note 1) and 5 g. of ethoxyethyne is refluxed. After about 1 hr. most of the solid material (tyrosine ester hydrochloride) has dissolved. The slightly yellow solution is cooled and diluted with 25 ml. of ethyl acetate. It is washed subsequently with 20 ml. of cold 0.5*N* hydrochloric acid, 20 ml. of cold 5% aqueous potassium carbonate, and finally with 20 ml. of water, then dried with sodium sulfate and evaporated *in vacuo* (bath temperature below 60°) (note 2).

The residue is dissolved in 35 ml. of cold acetone and mixed with 42 ml. of 1*N* aqueous potassium hydroxide. Some heat is evolved, and a clear solution is soon obtained. After 30 min. standing at room temperature, acetone is removed *in vacuo*, 50 ml. of water is added, and unsaponified oily materials are extracted with ether.

The aqueous phase is acidified by pouring into 15 ml. of 2*N* hydrochloric acid. An oil precipitates which soon crystallizes. The product, *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteinyl-L-tyrosine, is filtered and dried. Yield 8.3 g. It can be recrystallized from ethanol–water; m.p. 196–197°, $[\alpha]_D^{20}$ −24° (c = 0.8 in dimethylformamide).

Note 1: Commercial ethyl acetate is purified by twice washing 250 ml. with 50 ml. of 5% aqueous potassium carbonate, then twice with 30 ml. of water, drying by brief shaking with 15 g. of anhydrous sodium sulfate, and distilling. The material obtained in this way contains a little water, but this is advantageous for the reaction. In perfectly anhydrous ethyl acetate, the reaction rate is considerably lower and a yellow-brown color easily develops.

Note 2: At this stage many dipeptide esters can be purified by dissolving in hot ethyl acetate and diluting with warm light petroleum until a faint turbidity remains. The sample is then heated to the boiling point, when a clear solution is obtained. This is left at room temperature for crystallization. Several dipeptide esters, however, crystallize with difficulty and separate as viscous oils.

F. PREPARATION OF AN ACID ANHYDRIDE BY MEANS OF ETHOXYETHYNE (Vinylacetic Anhydride)

$$2CH_2{=}CHCH_2COOH + HC{\equiv}COC_2H_5 \longrightarrow (CH_2{=}CHCH_2CO)_2O + CH_3COOC_2H_5$$

A solution of 50 g. (0.71 mole) of ethoxyethyne in 50 ml. of absolute ether is added in 1 hr., dropwise and with stirring, to a solution of 86 g. (1 mole) of vinylacetic acid in 100 ml. of absolute ether. During this operation moisture must be excluded and the temperature kept at 10–15° by cooling in ice water. The mixture is left for 2 hr. additional in the cooling bath and then kept overnight at room temperature in a well-closed vessel. The solvent is subsequently removed by distillation through a 20 cm. Vigreux column. The bath temperature is kept below 60°. Distillation is continued *in vacuo*. After a forerun, vinylacetic anhydride distills at 88–92°/12 mm., n_D^{20} 1.4441. The yield is 55%. By redistillation of the forerun, a second crop may be obtained. Total yield 60–65%. The residue contains crotonic anhydride, b.p. 116°/12 mm., n_D^{20} 1.4744.

From the forerun some ethyl vinylacetate has been isolated.

Note 1: The yields of anhydrides obtained from stable acids are much higher and are sometimes nearly quantitative.

References

Russian publications could be consulted only partly in their original form. The papers which have been read as abstracts only are referred to by giving the abstract journal and (between parentheses) the original periodical.

1. M. Slimmer, *Ber.*, *36*, 289 (1903).
2. A. Sabanejeff and P. Dworkowitsch, *Ann.*, *216*, 283 (1882).
3. T. L. Jacobs, R. Cramer, and J. E. Hanson, *J. Am. Chem. Soc.*, *64*, 223 (1942).

3a. H. Scheibler, E. Marhenkel, and R. Nikolić, *Ann.*, *485*, 28 (1927).

3b. F. Montanari, *Gazz. chim. ital.*, *86*, 735 (1956).

4. W. E. Parham and P. L. Stright, 129th meeting, ACS, Dallas, Texas, April, 1956; *J. Am. Chem. Soc.*, *78*, 4783 (1956).

5. W. E. Truce, H. E. Hill, and M. M. Boudakian, *J. Am. Chem. Soc.*, *78*, 2760 (1956).
6. J. F. Arens and T. Doornbos, *Rec. trav. chim.*, *75*, 481 (1956).
7. E. Fromm, H. Benzinger, and F. Schäfer, *Ann.*, *394*, 325 (1912).
8. H. J. Backer and J. Strating, *Rec. trav. chim.*, *73*, 565 (1954).
9. N. A. Preobrazhenskiĭ and V. V. Shokina, *Zhur. Obshcheĭ Khim.*, *15*, 65 (1945).
10. *Chem. Abstr.*, *40*, 1793*i* (1946); compare also E. I. Genkin, *Chem. Abstr.*, *48*, 5835 (1954).
11. J. F. Arens and D. A. van Dorp, *Rec. trav. chim.*, *67*, 973 (1948).
12. D. A. van Dorp and J. F. Arens, *Nature*, *160*, 189 (1947).
13. M. N. Shchukina and I. A. Rubtsov, *Zhur. Obshcheĭ Khim.*, *18*, 1645 (1948).
14. M. Julia, *Compt. rend.*, *227*, 1374 (1948).
15. Sir Ian Heilbron, E. R. H. Jones, M. Julia, and B. C. L. Weedon, *J. Chem. Soc.*, *1949*, 1823.
16. J. F. Arens and P. Modderman, *Proc. Koninkl. Ned. Akad. Wetenschap.*, *53*, 1163 (1950).
17. G. Eglinton, E. R. H. Jones, B. L. Shaw, and M. C. Whiting, *J. Chem. Soc.*, *1954*, 1860.
18. J. F. Arens, *Rec. trav. chim.*, *74*, 769 (1955).
19. J. F. Arens, *Festschrift Arthur Stoll*, Sandoz A.-G., Basel, 1957, p. 468.
20. J. F. Arens, H. C. Volger, T. Doornbos, J. Bonnema, J. W. Greidanus, and J. H. van den Hende, *Rec. trav. chim.*, *75*, 1459 (1956).
21. T. L. Jacobs, R. Cramer, and F. T. Weiss, *J. Am. Chem. Soc.*, *62*, 1849 (1940).
22. A. E. Favorskiĭ and M. F. Shostakovskiĭ, *Chem. Abstr.*, *38*, 330 (1944) (*Zhur. Obshcheĭ Khim.*, *13*, 1 (1943)).
23. A. E. Favorskiĭ and M. N. Shchukina, *Chem. Abstr.*, *40*, 4347 (1946) (*Zhur. Obshcheĭ Khim.*, *15*, 385 (1945)).
24. A. E. Favorskiĭ and M. N. Shchukina, *Chem. Abstr.*, *40*, 4657 (1946) (*Zhur. Obshcheĭ Khim.*, *15*, 394 (1945)).
25. M. N. Shchukina, *Zhur. Obshcheĭ Khim.*, *18*, 1350 (1948).
26. M. F. Shostakovskiĭ and F. P. Sidel'kovskaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, *1950*, 641.
27. Y. R. Naves and P. Ardizio, *Bull. soc. chim. France*, *1951*, 374.
28. D. A. van Dorp, J. F. Arens and O. Stephenson, *Rec. trav. chim.*, *70*, 289 (1951).
29. J. Ficini, *Bull. soc. chim. France*, *1954*, 1367.
29a. J. Ficini and H. Normant, *Compt. rend.*, *237*, 731 (1953).
30. J. F. Arens, *Rec. trav. chim.*, *74*, 271 (1955).
31. L. F. Hatch and H. D. Weiss, *J. Am. Chem. Soc.*, *77*, 1798 (1955).
32. T. L. Jacobs and W. R. Scott, *J. Am. Chem. Soc.*, *75*, 5497 (1953).
33. E. R. H. Jones, G. Eglinton, M. C. Whiting, and B. L. Shaw, *Org. Syntheses*, *34*, 46 (1954).
34. O. Isler, M. Montavon, R. Rüegg, and P. Zeller, *Helv. Chim. Acta*, *39*, 259 (1956).
35. T. L. Jacobs and W. R. Scott, *J. Am. Chem. Soc.*, *75*, 5500 (1953).

36. M. F. Shostakovskiĭ and F. P. Sidel'kovskaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk, 1950*, 394.
37. Unpublished observations in the author's laboratory in Groningen.
38. M. F. Shostakovskii and F. P. Sidel'kovskaya, *Zhur. Obshcheĭ Khim., 20*, 620 (1950).
39. T. L. Jacobs, J. D. Roberts, and W. G. MacMillan, *J. Am. Chem. Soc., 66*, 656 (1944).
40. T. L. Jacobs and W. P. Tuttle, *J. Am. Chem. Soc., 71*, 1313 (1949).
41. T. L. Jacobs and W. J. Whitcher, *J. Am. Chem. Soc., 64*, 2635 (1942).
42. F. Montanari and A. Negrini, *Ricerca sci., 27*, 467 (1957).
43. E. Angeletti, F. Montanari, and A. Negrini, *Gazz. chim. ital., 87*, 1115 (1957).
44. H. C. Volger and J. F. Arens, *Proc. Koninkl. Ned. Akad. Wetenschap., B60*, 43 (1957).
45. F. Montanari, *Ricerca sci., 25*, 3107 (1955).
46. F. Montanari, *Gazz. chim. ital., 86*, 406 (1956).
47. R. C. Fuson, C. C. Price, R. A. Bauman, O. H. Bullitt, W. R. Hatchard, and E. W. Maynert, *J. Org. Chem., 11*, 469, 472 (1946).
48. E. Schneider, *Chem. Ber., 84*, 911 (1951).
49. H. Brintzinger, H. Schmahl, and H. Witte, *Chem. Ber., 85*, 338 (1952).
50. H. Brintzinger and H. Ellwanger, *Chem. Ber., 87*, 300 (1954).
51. N. Kharasch and S. J. Assony, *J. Am. Chem. Soc., 75*, 1081 (1953).
52. N. Kharasch and S. J. Assony, *J. Am. Chem. Soc., 77*, 3390 (1955).
53. F. Montanari and A. Negrini, *Boll. sci. fac. chim. ind., Bologna, 14*, 71 (1956).
54. F. Montanari and A. Negrini, *Gazz. chim. ital., 87*, 1073 (1957).
55. E. Angeletti, F. Montanari, and A. Negrini, *Gazz. chim. ital., 87*, 1086 (1957).
56. N. L. Owen and M. U. S. Sultanbawa, *J. Chem. Soc., 1949*, 3109.
57. W. J. Croxall, L. R. Freimiller, and E. Y. Shropshire, *J. Am. Chem. Soc., 72*, 4275 (1950).
58. A. Stoll, R. Morf, A. Rheiner, and J. Renz, *Experientia, 12*, 360 (1956).
59. E. Gryszkiewicz-Trochimowski, W. Schmidt, and O. Gryskiewicz-Trochimowski, *Bull. soc. chim. France, 1948*, 593.
60. H. J. Backer and A. E. Beute, *Rec. trav. chim., 54*, 167 (1935).
61. W. E. Truce and M. M. Boudakian, *J. Am. Chem. Soc., 78*, 2748 (1956).
62. W. Reppe *et al., Ann., 601*, 111 (1956).
63. W. E. Truce, J. A. Simms, and M. M. Boudakian, *J. Am. Chem. Soc., 78*, 695 (1956).
64. M. F. Shostakovskiĭ, *Chem. Abstr., 49*, 9483*f* (1955) (*Izvest. Akad. Nauk. S.S.S.R., Otdel Khim. Nauk, 1954*, 526).
65. C. C. Price and H. Morita, *J. Am. Chem. Soc., 75*, 4747 (1953).
66. F. Montanari, *Boll. sci. fac. chim. ind., Bologna, 14*, 55 (1956).
67. C. C. Price and R. G. Gillis, *J. Am. Chem. Soc., 75*, 4750 (1953).
67a. T. F. Doumani, U. S. Pat. 2,402,878 (June 25, 1946) (to Union Oil Co. of California).
68. L. Chierici and F. Montanari, *Gazz. chim. ital., 86*, 1269 (1956).
69. J. Nieuwenhuis and J. F. Arens, *Rec. trav. chim., 76*, 999 (1957).

70. H. Baganz and W. Triebsch, *Naturwissenschaften, 42,* 155 (1955); *Chem. Ber., 89,* 895 (1956).
71. E. Fromm and E. Siebert, *Ber., 55,* 1014 (1922).
72. E. Fromm and H. Landmann, *Ber., 56,* 2290 (1923).
73. W. E. Truce, M. M. Boudakian, R. F. Heine, and R. J. McManimie, *J. Am. Chem. Soc., 78,* 2743 (1956).
74. W. E. Truce and R. J. McManimie, *J. Am. Chem. Soc., 75,* 1672 (1953).
75. W. E. Truce and R. J. McManimie, *J. Am. Chem. Soc., 76,* 5745 (1954).
76. N. W. Cuza and H. McCombie, *J. Chem. Soc., 1937,* 767.
77. W. E. Parham and J. Heberling, *J. Am. Chem. Soc., 77,* 1175 (1955).
78. F. Montanari, *Gazz. chim. ital., 86,* 420 (1956).
79. F. Montanari, *Gazz. chim. ital., 86,* 747 (1956).
80. F. Montanari and A. Negrini, *Gazz. chim. ital., 87,* 1061 (1957).
81. G. Modena and F. Montanari, *Gazz. chim. ital., 86,* 432 (1956).
82. H. J. Backer, J. Strating, and J. F. A. Hazenberg, *Rec. trav. chim., 72,* 813 (1953).
83. H. C. Volger and J. F. Arens, *Rec. trav. chim., 77,* 1170 (1958).
84. J. C. W. Postma and J. F. Arens, *Rec. trav. chim., 75,* 1385 (1956).
85. J. C. W. Postma and J. F. Arens, *Rec. trav. chim., 75,* 1408 (1956); compare also J. C. W. Postma, thesis, Groningen, May, 1956.
86. N. B. Colthup, *J. Opt. Soc. Amer., 40,* 398 (1950).
87. J. Nieuwenhuis and J. F. Arens, *Rec. trav. chim., 77,* 761 (1958).
88. N. A. Preobrazhenskii and I. A. Rubtsov, *Zhur. Obshcheĭ Khim., 18,* 1719 (1948).
89. H. Heusser, K. Eichenberger, and Pl. A. Plattner, *Helv. Chim. Acta, 33,* 1088 (1950).
90. A. Caliezi and H. Schinz, *Helv. Chim. Acta, 33,* 1129 (1950).
91. D. Magrath, D. S. Morris, V. Petrow, and R. Royer, *J. Chem. Soc., 1950,* 2393.
92. G. R. Clemo and B. K. Davison, *J. Chem. Soc., 1951,* 447.
93. H. Brack and H. Schinz, *Helv. Chim. Acta, 34,* 2009 (1951).
94. A. Caliezi and H. Schinz, *Helv. Chim. Acta, 35,* 1637 (1952).
95. B. N. Feitelson and V. Petrow, *J. Chem. Soc., 1952,* 3358.
96. A. Caliezi and H. Schinz, *Helv. Chim. Acta, 35,* 1649 (1952).
97. H. Kappeler, H. Grütter, and H. Schinz, *Helv. Chim. Acta, 36,* 1862 (1953).
98. H. Kappeler, D. Stauffacher, A. Eschenmoser and H. Schinz, *Helv. Chim. Acta, 37,* 957 (1954).
99a. J. C. W. Postma, *Proc. Koninkl. Ned. Akad. Wetenschap., B58,* 130 (1955).
99b. J. C. W. Postma and J. F. Arens, *Rec. trav. chim., 75,* 1377 (1956).
100a. L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns, and J. M. Constantin, *J. Am. Chem. Soc., 74,* 4974 (1952).
100b. R. G. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer, and L. H. Sarett, *J. Am. Chem. Soc., 76,* 1715 (1954).
101. J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta, 40,* 1438 (1957); previous short communication: J. Schmidlin, G. Anner, J. R. Billeter and A. Wettstein, *Experientia, 11,* 365 (1955).

102. H. C. Brown, *J. Chem. Soc., 1956*, 1248.
103. J. F. Arens and D. A. van Dorp, *Rec. trav. chim., 68*, 604 (1949).
104. W. Graham, D. A. van Dorp, and J. F. Arens, *Rec. trav. chim., 68*, 609 (1949).
105. J. F. Arens and P. Modderman, *Proc. Koninkl. Ned. Akad. Wetenschap., B54*, 236 (1951).
106. H. Heusser, K. Eichenberger, and Pl. A. Plattner, *Helv. Chim. Acta, 33*, 370 (1950).
107. A. Rouvé and M. Stoll, *Helv. Chim. Acta, 33*, 2019 (1950).
108. M. Stoll and B. Willhalm, *Helv. Chim. Acta, 35*, 775 (1952).
109. H. Lindlar, *Helv. Chim. Acta, 35*, 446 (1952).
110. H. H. Inhoffen and D. Erdmann, *Ann., 598*, 51 (1956).
111. R. A. Raphael, *Acetylenic Compounds in Organic Synthesis*, Butterworths, London, 1955, p. 12.
112. A. Lardon, O. Schindler, and T. Reichstein, *Helv. Chim. Acta, 40*, 666 (1957).
113. C. Mannich and F. T. Chang, *Ber., 66*, 418 (1933).
114. A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc., 1957*, 5096.
115. E. A. Braude and O. H. Wheeler, *J. Chem. Soc., 1955*, 320.
116. Y. A. Sinnema and J. F. Arens, *Rec. trav. chim., 76*, 949 (1957).
117. T. L. Jacobs and S. Searles, *J. Am. Chem. Soc., 66*, 686 (1944).
118. Th. R. Rix and J. F. Arens, *Proc. Koninkl. Ned. Akad. Wetenschap., B56*, 368 (1953); compare also Th. R. Rix, thesis, Bandung, Indonesia, April, 1954.
119. L. Heslinga and J. F. Arens, *Rec. trav. chim., 76*, 982 (1957).
120. L. Heslinga, G. J. Katerberg, and J. F. Arens, *Rec. trav. chim., 76*, 969 (1957).
121. Th. R. Rix and J. F. Arens, *Proc. Koninkl. Ned. Akad. Wetenschap., B56*, 372 (1953).
122. R. Broekema, S. van der Werf, and J. F. Arens, *Rec. trav. chim., 77* (1958).
123. Y. A. Sinnema and J. F. Arens, *Rec. trav. chim., 74*, 901 (1955).
124. J. Nieuwenhuis and J. F. Arens, *Rec. trav. chim., 77*, 1153 (1958).
125. Y. A. Sinnema and J. F. Arens, *Rec. trav. chim., 75*, 1423 (1956); compare also Y. A. Sinnema, thesis, Groningen, March, 1957.
126. J. F. McKenna and F. J. Sorwa, *J. Am. Chem. Soc., 60*, 124 (1938).
127. Th. R. Rix and J. F. Arens, *Proc. Koninkl. Ned. Akad. Wetenschap., B56*, 364 (1953).
128. F. Beyerstedt and S. M. McElvain, *J. Am. Chem. Soc., 58*, 529 (1936).
128a. H. M. Barnes, D. Kundiger, and S. M. McElvain, *J. Am. Chem. Soc., 62*, 1281 (1940).
129. J. F. Arens and T. Doornbos, *Rec. trav. chim., 74*, 79 (1955).
130. J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc., 79*, 1262 (1957).
131. J. F. Arens, "Some Aspects of the Chemistry of Organic Sulfides," in N. Kharasch, ed., *Organic Sulfur Compounds*, Pergamon Press, Inc., New York, in press.
132. H. Vieregge and J. F. Arens, *Rec. trav. chim., 76*, 546 (1957).
133. J. F. Arens, D. H. Koerts, and P. Plieger, *Rec. trav. chim., 75*, 1454 (1956).
134. L. I. Smith and H. H. Hoehn, *J. Am. Chem. Soc., 61*, 2619 (1939); *63*, 1175 (1941).
135. J. F. Arens and Th. R. Rix, *Proc. Koninkl. Ned. Akad. Wetenschap., B57*, 275 (1954).

136. J. F. Arens and Th. R. Rix, *Proc. Koninkl. Ned. Akad. Wetenschap., B57,* 281 (1954).
137. J. F. Arens and Th. R. Rix, *Proc. Koninkl. Ned. Akad. Wetenschap., B57,* 270 (1954).
138. J. F. Arens, J. G. Bouman, and D. H. Koerts, *Rec. trav. chim., 74,* 1040 (1955).
139. W. Reppe, *Neue Entwicklungen auf dem Gebiet der Chemie des Acetylens und Kohlenoxyds,* Springer Verlag, Berlin, 1949, p. 21.
140. H. C. Volger, thesis, Groningen, June, 1958.
141. H. C. Volger and J. F. Arens, *Rec. trav. chim., 76,* 847 (1957).
142. J. F. Arens, A. C. Hermans, and J. H. Sperna Weiland, *Proc. Koninkl. Ned. Akad. Wetenschap., B58,* 78 (1955).
143. J. H. Sperna Weiland and J. F. Arens, *Rec. trav. chim., 75,* 1358 (1956).
144. J. H. Sperna Weiland and J. F. Arens, to be published in *Rec. trav. chim.*
145. R. B. Woodward and G. Small, *J. Am. Chem. Soc., 72,* 1298 (1950).
146. E. B. Reid and S. J. Groszos, *J. Am. Chem. Soc., 75,* 1655 (1953).
147. B. Eistert and W. Reiss, *Chem. Ber., 87,* 108 (1954).
148. F. H. Coats and R. C. Anderson, *J. Am. Chem. Soc., 79,* 1340 (1957).
149. J. Strating and H. J. Backer, *Rec. trav. chim., 73,* 709 (1954).
150. N. Juster, Ph.D. Thesis, University of California, Los Angeles, 1956.
151. A. W. Johnson, *J. Chem. Soc., 1946,* 1009.
152. H. H. Inhoffen, F. Bohlmann, and G. Rummert, *Ann., 569,* 226 (1950).
153. A. Auerhahn and R. Stadler (I. G. Farbenindustrie A.-G.), Ger. Pat. 601,822.
154. G. I. Samokhvalov, I. A. Rubtsov, M. A. Miropol'skaya, and N. A. Preobrazhenskiĭ, *Chem. Abstr., 50,* 4077*d* (1956) (*Trudy, Vsesoyuz. Nauch.-Issledovatel. Vitamin Inst., 4,* 10 (1953)).
155. F. Bohlmann, *Chem. Ber., 84,* 545 (1951).
156. M. Julia and J. M. Surzur, *Compt. rend., 238,* 2426 (1954).
157. M. Julia and J. M. Surzur, *Compt. rend., 238,* 1130 (1954).
158. G. Diab and M. Crauland (Soc. Anon. de St. Gobain), Fr. Pat. 1,090,421; *Chem. Zentr., 1957,* 13811.
159. Th. L. Jacobs, private communication; see K. Baum, Ph.D. Thesis, University of California, Los Angeles, 1957.
160. J. Queck, *Abhandl. braunschweig. wiss. Ges., 4,* 37 (1952).
161. F. Bohlmann, H. L. Ahrens, and H. Kritzler, *Abhandl. braunschweig. wiss. Ges., 9,* 173 (1957).
162. J. F. Arens, J. Vegter, and T. de Boer, *Rec. trav. chim., 77,* 753 (1958).
163. H. J. Panneman, A. F. Marx, and J. F. Arens, *Rec. trav. chim., 78,* 487 (1959).
164. J. C. Sheehan and J. J. Hlavka, *J. Am. Chem. Soc., 80,* 23, 635 (1958).
165. S. A. Szpilfogel, W. J. van der Burg, C. M. Siegmann, and D. A. van Dorp, *Rec. trav. chim., 77,* 157 (1958).
166. N. Vieregge and J. F. Arens, *Rec. trav. chim., 78,* 921 (1959).
167. F. Bohlmann and K. Kieslich, *Abhandl. braunschweig. wiss. Ges., 9,* 147 (1957).
168. R. L. Tse and M. S. Newman, *J. Org. Chem., 21,* 638 (1956).
169. M. S. Newman and G. R. Kahle, *J. Org. Chem., 23,* 666 (1958).

170. N. A. Milas and C. P. Priesing, *J. Am. Chem. Soc.*, *80*, 2189 (1958).
171. I. N. Nazarov, Zh. A. Krasnaya, and V. P. Vinogradov, *Chem. Abstr.*, *52*, 13611*g* (1958) (*Zhur. Obshchei Khim.*, *28*, 460 (1958)).
172. H. H. Wasserman and P. S. Wharton, *Tetrahedron*, *3*, 321 (1958).
173. J. Nieuwenhuis, thesis, Groningen, October, 1958.
174. B. Rosebeek and J. F. Arens, to be published.
175. J. R. Nooi and J. F. Arens, *Rec. trav. chim.*, *78*, 284 (1959).
176. H. J. Boonstra and J. F. Arens, *Rec. trav. chim.*, in press, 1960.
177. J. R. Nooi and J. F. Arens, to be published.
178. G. Vollema and J. F. Arens, *Rec. trav. chim.*, *78*, 140 (1959).
179. J. Cley and J. F. Arens, *Rec. trav. chim.*, *78*, 929 (1959).
180. H. Vieregge, H. J. T. Bos, and J. F. Arens, *Rec. trav. chim.*, *78*, 664 (1959).
181. H. J. T. Bos and J. F. Arens, to be published.
182. H. J. Boonstra, L. Brandsma, A. M. Wiegman, and J. F. Arens, *Rec. trav chim.*, *78*, 252 (1959).
183. J. Vegter and J. F. Arens, unpublished.
184. A M. Wiegman and J. F. Arens, unpublished.
185. W. Drenth and G. L. Hekkert, personal communication.
186. A. M. van Leusen and J. F. Arens, *Rec. trav. chim.*, *78*, 551 (1959).
187. G. Groenhuyzen and J. F. Arens, to be published.
188. P. Grünanger, *Atti accad. nazl. Lincei, Rend., Classe sci. fis., mat., e nat.*, [VIII] *24*, 163 (1958); see also P. Grünanger and M. R. Langella, *Gazz. chim. ital.*, *89*, 1784 (1959).
189. H. G. Viehe, *Chem. Ber.*, *92*, 1270 (1959).
190. W. Wisaksono and J. F. Arens, to be published.
191. T. L. Gresham, J. E. Jansen, F. W. Shaver, and W. L. Beears, *J. Am. Chem. Soc.*, *76*, 486 (1954).
192. H. J. Alkema and J. F. Arens, to be published.
193. W. Drenth, G. L. Hekkert, and B. G. Zwanenburg, personal communication.
194. F. A. Buiter and J. F. Arens, to be published.
195. L. Maioli and G. Modena, *Boll. sci. fac. chim. ind. Bologna*, *16*, 86 (1958).
196. G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Helv. Chim. Acta*, *42*, 1945 (1959).
197. H. Vieregge and J. F. Arens, to be published.
198. J. Bonnema and J. F. Arens, *Rec. trav. chim.*, in press, 1960.
199. W. Drenth, E. J. Stamhuis, and H. Hogeveen, personal communication.
200. W. E. Parham, R. F. Motter, and G. L. Mayo, *J. Am. Chem. Soc.*, *81*, 3386 (1959).

KETENE IN ORGANIC SYNTHESIS

By R. N. LACEY,* *The Distillers Company Ltd., Hull, England*

CONTENTS

I. Introduction 214
II. Reactions of Ketene 215
A. Reactions with Carboxylic Acids 215
B. Reactions with Hydroxyl Groups 216
C. Reactions with Thiols 217
D. Reactions with Amines, Amides, etc. 218
E. Reactions with Halogens and Halogen Compounds 219
F. Reactions with Hydrogen Cyanide 222
G. Reactions with Acetals, Orthoformates, and Ethers 223
H. Reactions with Carbonyl Compounds: Enol Acetylation 224
I. Reactions with Carbonyl Compounds: Formation of β-Lactones 226
J. Dimerization 229
K. Miscellaneous Reactions 229
III. Reactions of Isopropenyl Acetate 233
A. Reactions with Hydroxyl Groups 233
B. Reactions with Amines 234
C. Enol Acetylation of Aldehydes and Ketones 234
D. Reactions with Carboxylic Acids and Anhydrides 235
E. Miscellaneous Reactions 235
IV. Reactions of β-Propiolactone 236
A. Polymerization 236
B. Reactions with Hydroxyl Groups, etc. 237
C. Reactions with Amines 238
D. Reactions with Alkali Metal Salts 238
E. Miscellaneous Reactions 239
V. Reactions of Diketene 240
A. Constitution 240
B. Reactions with Hydroxyl Groups 241
C. Reactions with Amines, etc. 248
D. Miscellaneous Reactions 251
References 255

* Present address: BP Research Centre, The British Petroleum Company Ltd., Sunbury-on-Thames, England.

I. Introduction

Ketene, the first member of the class of compounds so closely linked with the name of H. Staudinger, was discovered by Wilsmore (256). It seems a happy chance that the first preparation of ketene, by the pyrolysis of acetic anhydride, was effected in 1907 by a method closely akin to the type of process used today on a large industrial scale, and, further, that this approximation to a technical method of preparation anticipated, albeit by only a few months, Staudinger's own synthesis (232) by the classical method of debromination of bromoacetyl bromide with zinc. The development of the chemistry of ketene and its derivatives since that time has continued to owe more to commercial than to academic inspiration. The importance of ketene and its derivatives in industry has led to the intensive exploration of the chemistry of ketene in industrial laboratories, although the experimental difficulties associated with the preparation and use of this reagent have resulted in a comparative neglect of this field in academic research.

Ketene is a gas at ordinary temperatures (b.p. −41°) which is readily converted to a dimer and higher polymers. It is, therefore, most conveniently freshly made as required and converted immediately. To this experimental difficulty must be added the hazard of handling ketene, which is an extremely poisonous gas, being of the same order of toxicity as phosgene. It confers an unpleasant characteristic taste to the mouth when traces are inhaled, which is particularly pronounced if the operator is smoking, and in larger amounts gives symptoms of shortage of breath and giddiness. It cannot be overemphasized that all operations with ketene in the laboratory should be conducted in an efficient fume chamber.

Ketene is made industrially either by the cracking of acetic acid at about 700°, generally under reduced pressure and in the presence of triethyl phosphate, or by the pyrolysis of acetone without catalyst at 700–800°. The latter method is generally used in the laboratory and the equipment, consisting essentially of an electrically heated filament of nickel–chromium wire suspended in acetone vapor, has been fully described elsewhere (120). Ketene so obtained contains much inert gas which may, in some reactions, hinder absorption; in such cases, the cracking of acetic anhydride, for which experimental details of a laboratory scale apparatus have been published (77), may prove preferable. If diketene is available, this may readily be

cracked in the same type of apparatus as is used for the pyrolysis of acetone to give ketene of 80–85% purity at a high rate.

$$CH_3CO_2H \longrightarrow CH_2{:}C{:}O + H_2O$$

$$CH_3COCH_3 \longrightarrow CH_2{:}C{:}O + CH_4$$

$$(CH_3CO)_2O \longrightarrow CH_2{:}C{:}O + CH_3CO_2H$$

Ketene serves as a valuable acetylating agent for alcohols, amines, acids, etc., and under the best conditions gives high yields. Furthermore, in many cases, despite the practical difficulties associated with its use, it is the best choice, being particularly suitable for the selective acetylation of amines. The more interesting synthetic potentialities of ketene, however, are to be found in other applications. This review therefore emphasizes the acetylation of enolizable carbonyl compounds with ketene and the chemistry of isopropenyl acetate, the most widely studied product of this reaction; the reaction of carbonyl compounds with ketene in the presence of suitable catalysts to give β-lactones, with special reference to β-propiolactone, the simplest member of the series; and the chemistry of diketene.

Earlier reviews include those of Hagemeyer (103) and Quadbeck (209) on ketene chemistry, Hagemeyer and Hull (118) on isopropenyl acetate, an excellent review by Zaugg (266) on β-lactones, and articles by Hanford and Sauer (120) and Boese (26) on diketene.

II. Reactions of Ketene

A. REACTIONS WITH CARBOXYLIC ACIDS

From a practical and industrial standpoint the most important reaction of ketene is that with carboxylic acids to give acid anhydrides.

$$RCO_2H + CH_2{:}C{:}O \longrightarrow RCO_2COCH_3$$

The conversion of acetic acid to acetic anhydride by treatment with ketene is used on a very large scale, particularly in the cellulose acetate industry, in which it is necessary to provide acetic anhydride for acetylation from the acetic acid arising as by-product of that reaction. Ketene reacts readily in the absence of catalysts with other carboxylic acids to give mixed anhydrides which may disproportionate to the

simple anhydrides (71,133,251). The reaction may be carried out without solvent or in an inert diluent such as benzene, acetone, or ether. Thus, benzoic acid gives the mixed anhydride with ketene in quantitative yield; distillation *in vacuo*, however, leads to complete conversion to acetic anhydride and benzoic anhydride. The method has been used for the preparation of the anhydrides of higher aliphatic acids (252).

$$2CH_3CO_2COR \longrightarrow (RCO)_2O + (CH_3CO)_2O$$

With formic acid the stable anhydride is formed; this can easily be distilled (71,138). This derivative reacts with amino groups to give almost exclusively formyl derivatives (138). The reactions of the mixed anhydride obtained from the reaction of ketene and chloroacetic acid with aromatic amines have been studied by Emery and Gold (72); they found that in benzene the anhydride reacted with aniline to give mainly the chloroacetyl derivative, whereas in the more polar medium, 50% aqueous acetone, the product was mainly the acetyl derivative.

B. REACTIONS WITH HYDROXYL GROUPS

$$ROH + CH_2{:}C{:}O \longrightarrow ROCOCH_3$$

The reaction of ketene with water to give acetic acid was observed by Wilsmore (256), but the reaction is slow and water is a poor absorbent for ketene. The addition of catalysts, particularly strong acids, is necessary for a satisfactory rate of reaction; ketene is readily absorbed by dilute aqueous acetic acid. Hydrogen peroxide is more readily acetylated to give diacetyl peroxide (8); isolation of the intermediate peracetic acid is not practicable.

The literature relating to the use of ketene for the acetylation of aliphatic hydroxyl groups is very extensive, but much of it relates to largely unsuccessful attempts to use ketene for the acetylation of carbohydrates, particularly cellulose. The lower aliphatic alcohols can be acetylated, but it is difficult to obtain a complete conversion to acetate. Morey (180) found that a mixture of 75% *n*-butyl acetate and *n*-butanol was not further acetylated in the absence of catalysts. Various materials have been proposed as catalysts for the reaction of ketene with alcohols. The most effective are acids such as sulfuric acid (180), *p*-toluenesulfonic acid (138), potassium hydrogen sulfate

(203), and perchloric acid (119). Suitable quantities of these catalysts lie in the range 0.2–1.0%. The use of "acidic" suspended catalysts such as silica–alumina-zirconia has been claimed (40). With acid catalysts such as sulfuric acid or *p*-toluenesulfonic acid, *tert*-butanol may readily be acetylated (138,180), whereas, in the absence of catalysts, the reaction is slow and is accompanied by the partial polymerization of the ketene. Basic catalysts including sodium acetate (204) and pyridine (131) have also been used. The acetylation of hydroperoxides with ketene has been described (14).

Variable results have been reported from attempts to acetylate phenol with ketene (7,213). Successful acetylation may, however, be achieved by the use of acid catalysts such as described in the previous paragraph (138). Ketene exhibits no advantages over conventional agents for the acetylation of phenols; whereas resorcinol may be smoothly acetylated in the presence of sulfuric acid with ketene, phloroglucinol is acetylated only slowly under such conditions (145). Salicylic acid with ketene was found by Rice *et al.* (213) to give a mixed anhydride, contrary to the claim of van Alphen (7) who reported having obtained acetylsalicylic acid, which had apparently arisen as a result of the hydrolysis of the primary product during the course of recrystallization from an aqueous medium.

C. REACTIONS WITH THIOLS

$$RSH + CH_2{:}C{:}O \longrightarrow RSCOCH_3$$

Wilsmore and Chick allowed ketene to react with hydrogen sulfide in the liquid state and obtained thioacetic anhydride (257). Interaction of the reactants in the vapor phase over alumina at 100° has been claimed (54) to give thioacetic acid in high yield. Hurd and Williams (141) first tested Staudinger's (231) prediction that ketene would react with thiols by the preparation of ethyl thioacetate from ketene and ethanethiol. By allowing the reactants to stand for three days at −80°, a 92.6% yield was obtained. More recent work has shown that the reaction may be carried out at room temperature in carbon tetrachloride witn gaseous ketene and in the presence of catalytic quantities of sulfuric acid (70). Since, however, the yields reported were quite low, the value of these experimental conditions is doubtful. It has been reported that *tert*-mercaptans may not be acetylated even in the presence of catalysts (70), although Crouch

(53) has claimed an 89% yield of *tert*-butyl thioacetate from ketene and *tert*-butyl mercaptan. Cysteine reacts readily with ketene in slightly alkaline solution to give the *N*,*S*-diacetyl derivative (191). *N*-Acetylcysteamine ($CH_3CONHCH_2CH_2SH$) is acetylated smoothly in ether to give a 96% yield of *N*,*S*-diacetylcysteamine (156).

D. REACTIONS WITH AMINES, AMIDES, ETC.

The reaction of ketene with primary amines is a general one which proceeds very rapidly and gives high yields of product:

$$RNH_2 + CH_2{:}C{:}O \longrightarrow RNHCOCH_3$$

aqueous media can often be used and catalysts are unnecessary. Bergmann and Stern (18) were able to acetylate many amino acids in an aqueous medium with ketene. Such acids may be acetylated as their sodium salts in aqueous solution to give high yields, but aminoacetic acid and leucine were readily acetylated even in the absence of alkali; *l*-tyrosine was converted under these conditions to the *O*,*N*-diacetyl derivative. Amino alcohols (205) and aminophenols (19) may be acetylated with ketene to give exclusively *N*-acetylation. Thus, serine and glucosamine (19) gave *N*-acetyl derivatives on treatment with ketene. Insulin (236) and other proteins having amino and hydroxyl groups can be acetylated stepwise, the acetylation with ketene being, in general, controllable to give *N*-acetylation only, although some doubt has been expressed (171) that *N*-acetylation can always be accomplished without attack on the tyrosine hydroxyl group.

Secondary aliphatic amines also react readily with ketene, but secondary aromatic amines, due to their lower basic strength, are rather slow to react. A 75% yield of *N*-acetyl-*N*-methylaniline was obtained by treatment of the amine with ketene in aqueous ethanol (19). Diphenylamine (127; cf. 238) in ether at 0° gave only a 33% yield of amide. Ethyleneimine readily reacts with ketene to give the expected *N*-acetyl derivative (21).

Van Alphen (6) found that ketene reacts with aryl hydrazines to give the expected 1-aryl-2-acetylhydrazines and with methylhydrazine to give 1-methyl-1,2-diacetylhydrazine. The reaction of ketene with hydroxylamine was shown to give acetylhydroxamic acid (132). Further acetylation of hydroxamic acids (RCONHOH) involves, first, *O*-acetylation to give $RCONHO_2CCH_3$ followed by facile *N*-

acetylation on addition of a further molecule of ketene to give a diacetylhydroxamic acid ($RCON(COCH_3)O_2CCH_3$).

Ketene reacts sluggishly with acetamide to give an oil, possibly $MeC(OCOCH_3):NCOCH_3$, which on standing affords diacetamide (56% yield (194)). Further reaction with ketene can give triacetamide which is a powerful acetylating agent. Acid catalysts, such as sulfuric acid, phosphoric acid, or benzenesulfonic acid, promote the reaction of ketene with amides (194,221). Ketene can also react with amides in the role of a dehydrating agent; treatment of sebacamide with two moles of ketene per mole of amide at 400° gives a 73% conversion to sebaconitrile (104). Svetkin and Forostyan (239) have acetylated thiourea with ketene, but, since the experiment was carried out in the presence of small amounts of acetic acid or water, the true acetylating agent may well have been acetic anhydride. Phthalimide and succinimide were not attacked by ketene (238).

Haloamines react in a complex manner. Useful yields of products have been recorded in three instances (52). Monochloroamine gave *N*-chloroacetamide in 70–75% yield. Dibromoamine gave bromoacetamide in 18% yield, the expected *N*-bromine having been replaced by hydrogen under the influence of hydrobromic acid in the reaction mixture. Nitrogen trichloride gave chloroacetamide in 14% yield, *N*-halogen atoms having again been replaced by hydrogen.

The nature of the complex yellow compound obtained by Wollenberg (261) from the reaction of ketene with pyridine has recently been elucidated (20).

E. REACTIONS WITH HALOGENS AND HALOGEN COMPOUNDS

$$CH_2{:}C{:}O + X_2 \longrightarrow XCH_2COX$$

The preparation of chloroacetyl chloride by the combination of ketene and chlorine has been regarded as so well established (26) as to be found in many textbooks. Recently it has been shown that the reaction, either in the vapor phase or in the liquid phase in many reaction media, gives a product which contains substantial amounts (20–30%) of the close-boiling dichloroacetyl chloride (167,206). The formation of this by-product may be repressed by chlorination in the vapor phase in the presence of an excess of ketene (167). The choice of medium for liquid phase chlorination is critical if formation of dichloroacetyl chloride is to be avoided. It has been confirmed

that the product obtained in 37% yield by Dashkewich (57) on chlorination in ether is free from dichloroacetyl chloride. Recent work (73) has shown that liquid sulfur dioxide at −12 to −24° may be used and makes possible 75% yields; possibly the true chlorinating agent is sulfuryl chloride, since the presence of only a minor amount of sulfur dioxide is effective in suppressing the formation of dichloroacetyl chloride. Alkyl acetates have also, rather surprisingly, been found to provide satisfactory reaction media, and 75–80% yields of chloroacetyl chloride free from dichloroacetyl chloride have been obtained (158).

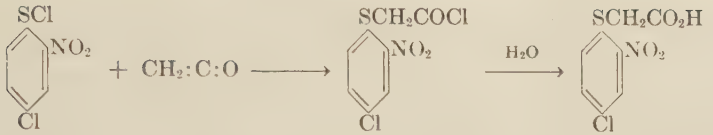
Bromine has been reported to react with ketene to give a small yield of bromoacetyl bromide (57,256). The vapor phase combination of these reactants in a flow system, into which ethanol is injected at a suitable point, has been described as a suitable method for the preparation of ethyl bromoacetate (50). The combination of iodine monochloride with ketene in carbon tetrachloride at −10 to −15° has been reported to give iodoacetyl chloride (217).

Hydrogen chloride readily gives acetyl chloride with ketene (257); the vapor phase combination over a carbon or silica gel catalyst has been described (74). Sulfuryl chloride combines with ketene to give chloroacetyl chloride and sulfur dioxide (225). With sulfur dichloride, according to one account, ketene gives polymers (225): in carbon tetrachloride at −20°, however, it is claimed that $S(CH_2COCl)_2$ is formed (15). The reaction of ketene with thionyl chloride in sulfur dioxide followed by treatment of the acid chloride formed with methanol gives I; with sulfur monochloride in chloroform, followed by addition of methanol, II is formed; ethylsulfenyl chloride in sulfur dioxide reacts with ketene and the intermediate with ethanol gave III (225). 2-Nitro-4-chlorophenylsulfenyl chloride reacts with ketene at 0° in chloroform to give, after hydrolysis of the product, the mercaptoacetic acid (IV) in 61% yield (214). Nitrosyl chloride

$$SOCl_2 + 2CH_2{:}C{:}O \longrightarrow OS(CH_2COCl)_2 \xrightarrow{MeOH} OS(CH_2CO_2Me)_2 \quad (I)$$

$$S_2Cl_2 + 2CH_2{:}C{:}O \longrightarrow S_2(CH_2COCl)_2 \xrightarrow{MeOH} S_2(CH_2CO_2Me)_2 \quad (II)$$

$$EtSCl + CH_2{:}C{:}O \longrightarrow EtSCH_2COCl \xrightarrow{EtOH} EtSCH_2CO_2Et \quad (III)$$



(IV)

with ketene gives chloroacetyl chloride (260); nitryl chloride (NO_2-Cl) gives chloroacetyl chloride and some nitroacetyl chloride (NO_2-CH_2COCl) (235).

Certain reactive organic chloro compounds react with ketene. Chlorobenzyl methyl ether condenses with ketene (used in large excess) at room temperature in the absence of catalyst to give V in 70% yield. α,β-Dichlorodiethyl ether requires the presence of 10% of aluminum trichloride for reaction and gives, after treatment of the product with ethanol, a 43% yield of VI (24). The reaction of chloromethyl methyl ether with ketene in the presence of Friedel-Crafts catalysts, followed by treatment with ethanol, has been claimed to give ethyl β-methoxypropionate (233). Triphenylmethyl chloride does not react with ketene in benzene solution at 50–60°, but, in the presence of aluminum trichloride at room temperature, followed by the addition of water, a 35% yield of VII (R = H) may be obtained (24). When benzene was replaced as solvent by the more highly polar nitrobenzene, no catalyst was necessary and VII (R = C_2H_5) was obtained in 67% over-all yield.

$$PhCHClOMe + CH_2{:}C{:}O \longrightarrow PhCH(OMe)CH_2COCl$$
(V)

$$ClCH_2CHClOEt + CH_2{:}C{:}O \longrightarrow ClCH_2CH(OEt)CH_2COCl \xrightarrow{EtOH} ClCH_2CH(OEt)CH_2CO_2Et$$
(VI)

$$Ph_3CCl + CH_2{:}C{:}O \longrightarrow Ph_3CCH_2COCl \xrightarrow[\text{or EtOH}]{H_2O} Ph_3CCH_2CO_2R$$
(VII)

Chloro compounds, such as benzyl chloride, benzotrichloride, and chloroacetone, and simple acid chlorides, such as benzoyl chloride and propionyl chloride, do not react with ketene (24,214). Šorm, Smrt,

and their colleagues (226,227) have shown that the ease of reaction of acid chlorides (RCOCl) falls in the following sequence: R = CH_2-COCl, CCl_3, COCl, CO_2Et, $CHCl_2$, COMe, CH_2Ph. Ketene is passed into a solution of the acid chloride in chloroform, or, better, sulfur dioxide (227), and the resultant product is treated with ethanol to esterify the acid chloride groupings. The general reaction is represented below, where R = CH_2COCl, CCl_3, $CHCl_2$, CO_2Et, and COCl. In the case where R = CCl_3, the use of an excess of ketene, treatment with ethanol being omitted, gives IX, which on melting loses hydrogen chloride to give X (R = CCl_3). VIII (R = EtO_2C) gives, after treatment with ethanol, X (R = EtO_2C) in addition to EtO_2CCO-CH_2CO_2Et.

$$RCOCl + CH_2{:}C{:}O \longrightarrow RCOCH_2COCl$$

(VIII)

$Cl_3CCOCH_2COCH_2COCl$ $\qquad$ $RC{:}CHCOCH_2COO$

(IX) $\qquad$ (X)

Other reactive compounds include malonyl chlorides of general formula $RR'C(COCl)_2$ where R = H, R′ = Ph; R = H, R′ = Ph-CH_2; R = R′ = Cl; R = H, R′ = $CH_2{:}CHCH_2$ (228). The products obtained with ketene were treated with ethanol to give keto-esters of the general formula $RR'C(CO_2Et)COCH_2CO_2Et$.

F. REACTIONS WITH HYDROGEN CYANIDE

Wilsmore and Chick (257) first studied the reaction of ketene with hydrogen cyanide and observed that the product was not acetyl cyanide. Later, with Deakin, Wilsmore (260) showed that the reaction gave 1-cyanovinyl acetate (XI), formed by the acetylation of the enol form of acetyl cyanide and identified by its reactions with water, alcohol, and aniline to give acetic acid, ethyl acetate, and acetanilide, respectively, with the elimination of hydrogen cyanide in all cases. The reaction has been shown to proceed well at −20 to 10° in solvents such as esters, ethers, etc., acetic anhydride being particularly suitable, and in the presence of basic catalysts such as *tert*-amines and sodium acetate (103,147,249). In the absence of catalysts, the reaction is accompanied by much diketene formation (103). Šorm and Smrt (223) prefer the use of much lower temperatures

(−60 to −70°), and it has been observed that at 10–30° 1,1-dicyanoethyl acetate (XII) is formed, presumably by the dimerization of acetyl cyanide.

$$CH_2{:}C{:}O + HCN \longrightarrow CH_3COCN \rightleftharpoons CH_2{:}C(OH)CN$$

$$CH_2{:}C(OH)CN + CH_2{:}C{:}O \longrightarrow CH_2{:}C(CN)O_2CCH_3 \quad (XI)$$

$$2CH_3COCN \longrightarrow CH_3C(CN)_2O_2CCH_3 \quad (XII)$$

1,1-Dicyanoethyl acetate may be formed almost to the exclusion of XI by carrying out the reaction with hydrogen cyanide as a 50% solution in acetic acid at 0° in the presence of 0.3% sodium acetate as catalyst (103). 1,1-Dicyanoethyl acetate has become of importance as an intermediate for the production of vinylidene cyanide which may be polymerized to form the basis of a valuable fiber-forming material, and much work has been devoted to its preparation. The reaction of ketene and hydrogen cyanide at 300–400° over a variety of catalysts has been described (9,215); good yields of acetyl cyanide were obtained by Roy (215) with a carbon catalyst, whereas in closely similar experiments Ardis and Stewart (9) obtained the dimer (XII). Conversions of 90–95% to XII have been claimed by the vapor phase reaction at 250° in the presence of triethylamine over activated alumina (237).

G. REACTIONS WITH ACETALS, ORTHOFORMATES, AND ETHERS

Ketene reacts with acetals in the presence of catalysts such as sulfuric acid, zinc chloride, or, particularly, boron trifluoride etherate, at −60 to −80° to give good yields of 3-alkoxy esters. Dimethoxymethane, for instance, gives methyl 3-methoxypropionate (36,224). Orthoformic esters react analogously to give 3,3-dialkoxy esters (101,224). Ketals and tetraethoxymethane fail to react (224).

$$CH_2(OMe)_2 + CH_2{:}C{:}O \longrightarrow MeOCH_2CH_2CO_2Me$$

$$CH(OEt)_3 + CH_2{:}C{:}O \longrightarrow (EtO)_2CHCH_2CO_2Et$$

Šorm and Smrt (224) have obtained yields of 80% and 92%, respectively, in the two cases illustrated above.

Ethers are normally inert to ketene, but ketene reacts with tetrahydrofuran in the presence of boron trifluoride to give a small yield of ω-caprolactone (102).

H. REACTIONS WITH CARBONYL COMPOUNDS: ENOL ACETYLATION

The reaction of ketene with enolizable carbonyl compounds to give enol esters was first reported by Degering and Gwynn (60). They found that treatment of acetone (1 mole) containing 0.007 mole of sulfuric acid at 55° with 0.81 mole of ketene gave a 45% conversion to isopropenyl acetate (XIII); elsewhere, the same authors claim a 73% yield (61).

$$CH_3COCH_3 + CH_2{:}C{:}O \longrightarrow CH_2{:}CMeO_2CCH_3$$
(XIII)

It was assumed that enolization of the ketone was the first step in the reaction mechanism, followed by acetylation of the enol hydroxyl. Higher temperatures were shown to favor good yields of enol esters. Later workers have claimed the use of other catalysts: halogen sulfonic acids, sulfamide acids, alkyl sulfonic acids (2,59,64), sulfocarboxylic acids (262), various sulfonated organic materials (sawdust, etc.) as suspended catalysts (263), acetylsulfoacetic acid (107), phosphorus oxychloride (42), and naphthalenesulfonic acids (176) have been described as effective.

Degering and Gwynn (61), in addition to their experiments on the enol acetylation of such simple ketones as acetone and acetophenone, also observed the acid-catalyzed reaction of ketene with α,β-unsaturated ketones. Mesityl oxide gives 2-acetoxy-4-methyl-1,3-pentadiene on treatment with ketene at 75° in the presence of 0.2% of sulfuric acid (62). Similarly, the acetylation of other α,β-unsaturated ketones, e.g., methyl vinyl ketone and ethylidene acetone, has been described by Hagemeyer (107).

Keto esters may be enol-acetylated with ketene. Both ethyl acetoacetate and ethyl levulinate in the presence of sulfuric acid at temperatures in the range 60–115° are *O*-acetylated in fair yields to isomer mixtures (63,64,134), e.g.,

$$CH_2{:}C{:}O + CH_3COCH_2CH_2CO_2Et \longrightarrow \begin{cases} CH_2{:}C(OAc)CH_2CH_2CO_2Et \\ CH_3C(OAc){:}CHCH_2CO_2Et \end{cases}$$

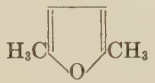
Degering and Spence have reported that the reaction of ketene with ethyl acetoacetate in the presence of *tert*-amines gives, in addition to *O*-acetylation, some Ac_2CHCO_2Et and $CH_3C(OAc):CAcCO_2Et$ (66). According to Isoshima (144) ketene reacts with ethyl acetoacetate in the absence of catalysts at 50° to give *C*-acetyl derivatives; in the presence of sulfuric acid at 80–90°, however, solely the mixed *O*-acetyl derivatives are formed in 67% yield.

Acetylacetone may readily be enol-acetylated with ketene in the presence of sulfuric acid to give 4-acetoxy-3-penten-2-one in 59% yield (63,134).

$$CH_3COCH_2COCH_3 + CH_2{:}C{:}O \longrightarrow CH_3C(OAc){:}CHCOCH_3$$

Diacetyl gives an enol acetate in only poor yield (63), but acetonylacetone is smoothly converted to 2,5-dimethylfuran (134).

$$CH_3COCH_2CH_2COCH_3 + 2CH_2{:}C{:}O \longrightarrow$$



Aldehydes may also be enol-acetylated with ketene, but the reaction is far less successful than with ketones. The lower aliphatic aldehydes such as acetaldehyde, propionaldehyde, and *n*-butyraldehyde react with ketene in the *absence* of catalyst at room temperature to give α,β-unsaturated ketones in 50–65% yield (2,103). The reaction mechanism presumably involves first the formation of diketene which subsequently reacts with aldehydes as described in detail in Section V-D-6.

$$2CH_2{:}C{:}O + RCHO \longrightarrow RCH{:}CHCOCH_3 + CO_2$$

TABLE I

Conversion of Ketene on Reaction with Aldehydes (Sulfuric Acid Catalyst)

Compound	Per cent converted to	
	Enol acetate	Unsatd. ketone
Acetaldehyde	21	17
Propionaldehyde	18	34
n-Butyraldehyde	7	51

This reaction, which is not observed with ketones, also takes place to some extent in the presence of acid catalysts, and, consequently, enol acetylation of aldehydes is accompanied by the formation of α,β-unsaturated ketones, which increase in proportion with increasing molecular weight of the aldehyde (103,126) (Table I).

α,β-Unsaturated aldehydes may be enol-acetylated with ketene with fair success; Agett (2) has reported a 36% yield of 1-acetoxy-1,3-butadiene from crotonaldehyde.

I. REACTIONS WITH CARBONYL COMPOUNDS: FORMATION OF β-LACTONES

In the presence of suitable catalysts ketene adds to the carbonyl group of aldehydes and ketones to give β-lactones.

$$RCOR' + CH_2{:}C{:}O \longrightarrow \begin{matrix} RR'C & \!\!-\!\!- & O \\ | & & | \\ CH_2 & \!\!-\!\!- & CO \end{matrix}$$

The industrial importance of β-propiolactone has resulted in a considerable literature on this condensation which has been reviewed elsewhere (103,266). Hagemeyer (103) has pointed out that suitable catalysts are generally salts which are strongly acid in aqueous solutions and capable of forming coordination complexes with hydroxyl groups. Although the Friedel-Crafts type of catalyst (157), such as boron trifluoride, aluminum trichloride, and zinc chloride in the form of complexes, are effective and among the best, many suitable catalysts lie outside this classification. Boric acid and triethyl borate (108); mercuric chloride (109) and other chlorides such as uranyl chloride (43) and those of tin, titanium, and iron (234); zinc thiocyanate and zinc nitrate (41); suspensions of oxides of aluminum, zirconium, thorium, silicon, etc. (117); acid-activated clays (265); perchlorates (39); salts of organic acids with nickel, barium, copper, and mercury (110); fluoborates (111); zinc trifluoracetate (44); and benzoyl peroxide (12) have been claimed as catalysts.

For the condensation of ketene with aldehydes, the less active catalysts, such as boric acid, zinc thiocyanate, and zinc chloride, suffice; alkyl borates and ortho- and metaphosphates are valuable in that they need not be destroyed at the end of the reaction. Ke-

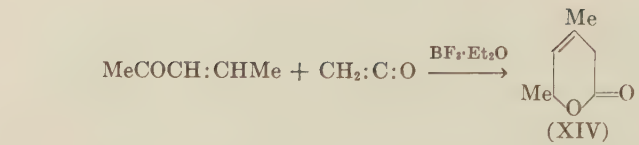
tones are less reactive; indeed, the reactions with the highly reactive acetaldehyde and formaldehyde may conveniently be carried out in ketonic diluents without interference. For the condensation of ketene with ketones, more active catalysts such as boron trifluoride etherate, zinc fluoborate, zinc fluophosphate, and mercuric chloride are required. The reactions with aldehydes may be carried out in ethers, ketones, or—in industrial practice—in a medium consisting of the β-lactone to be formed; β-lactones from ketones are generally prepared without solvents. The ready polymerization of β-lactones in the presence of the catalysts used requires the use of temperatures below about 25° for their preparation.

The condensation of ketene with ketoesters has been studied, the products being in general not isolated as such but examined by pyrolysis, hydrolysis, and alcoholysis procedures (112). The ease of formation of the β-lactone increases as the carbonyl group is further removed from the carboxyl group, i.e., from pyruvic ester to levulinic ester. Ketene has been condensed with diacetyl, acetylacetone, and acetonylacetone in the presence of $BF_3 \cdot Et_2O$ to give, in each case, both the mono- and di-β-lactones in poor yields. The products have been studied by thermal decarboxylation to unsaturated ketones and dienes, respectively, as illustrated below for the reaction with diacetyl (103).

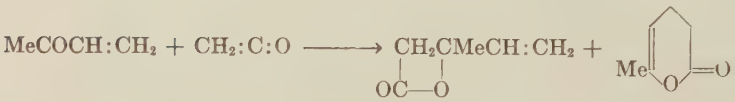
$$MeCOCOMe + CH_2{:}C{:}O \longrightarrow$$

$$\begin{cases} CH_2CMeCOMe \xrightarrow{-CO_2} CH_2{:}CMeCOMe \\ \quad\quad | \quad\quad | \\ \quad OC{-}{-}O \\ CH_2CMeCMeCH_2 \xrightarrow{-2CO_2} CH_2{:}CMeCMe{:}CH_2 \\ \quad\quad | \quad\quad | \quad\quad | \quad\quad | \\ \quad OC{-}O \quad\quad O{-}CO \end{cases}$$

The reaction of ketene with α,β-unsaturated aldehydes and ketones is complex. The β-alkyl vinyl ketones such as ethylidene acetone, mesityl oxide, and butylidene acetone do not react with ketene in the absence of a catalyst but in the presence of $BF_3 \cdot Et_2O$ give β,γ-unsaturated δ-lactones (e.g., XIV) in high yields (264). Vinyl ketones such as methyl vinyl ketone and methyl isopropenyl ketone (103,113), however, in the presence of zinc chloride give a mixture of products comprising a β-lactone and a γ,δ-unsaturated δ-lactone (e.g., XV). Methyl vinyl ketone is reported to react with ketene in the absence of of catalyst to give XV exclusively (125).



(XIV)



(XV)

α,β-Unsaturated aldehydes are also converted to a mixture of lactones by treatment with ketene in the presence of catalysts. The nature of the dienes formed on pyrolytic decarboxylation of the product from crotonaldehyde and ketene condensed at 0–10° has been taken to suggest that a mixture of predominantly the β-lactone with some δ-lactone (in a ratio of 1 : 10 of β-lactone) is formed (103). Condensation at a higher temperature gives a polymer which may be converted in good over-all yield to sorbic acid (see Section IV-A).

Benzaldehyde and acetophenone react with ketene in the presence of boric acid or zinc chloride at 0–10°; decarboxylation of the products gives fair yields of styrene and α-methylstyrene respectively, indicating the presence of β-lactones in the products (103). Hurd and Thomas (140) found the reaction of ketene with benzaldehyde, *m*-nitrobenzaldehyde, and furfural in the presence of potasssium acetate to give, as the main isolable products, the mixed anhydrides of acetic acid with the α,β-unsaturated acids expected from the hypothetical β-lactones, e.g.,

$$PhCHO + 2CH_2{:}C{:}O \longrightarrow PhCH{:}CHCO_2COMe$$

Hagemeyer (103) used sodium acetate at 60° and, after destructive distillation, obtained fair yields of furanacrylic acid and cinnamic acid from furfural and benzaldehyde, respectively, and converted the β-lactone from furfural to 3-(α-tetrahydrofuran)propionic acid (114) by hydrogenation. Hurd and Williams (141) converted cinnamaldehyde to PhCH:CHCH:$CHCO_2COMe$ with ketene in the presence of sodium acetate; this catalyst was found to be ineffective with ketones and aliphatic aldehydes (see also ref. 255) but has been used to catalyze the reaction of ketene with acrolein at −30° in ether to give 1,3-butadiene-1-carboxylic acid (80).

J. DIMERIZATION

Wilsmore and Chick (258) first observed the formation of diketene from ketene shortly after Wilsmore's discovery of the latter (see Section V). The ready dimerization of ketene is a reaction familiar to all workers with ketene and, indeed, diketene is frequently obtained as a by-product in slow reactions with ketene. Rice and Greenberg (212) have shown that ketene does not dimerize in the vapor phase at room temperature; the reaction takes place on points on the vessel surface and proceeds rapidly in droplets of liquid diketene once these are formed. The dimerization does not take place at $-80°$ at which temperature liquid ketene can be safely stored, but the reaction is quite rapid at 0°. Since it is unaffected by antioxidants or peroxides, the reaction is not a free-radical one but proceeds through an ionic mechanism. Bimolecular kinetics were observed with higher velocity constants in polar media, such as acetone, than in hydrocarbons.

In technical processes the reaction is carried out in absorption towers; diketene (181) or acetone (45) are used as reaction media in which the ketene dissolves and is subsequently dimerized (103). No catalysts are employed, and the temperatures used are up to 40–50°, giving yields which are claimed to be 90–95%. A suitable laboratory scale preparation has been described giving 50–55% yields (253).

K. MISCELLANEOUS REACTIONS

1. Reactions with Inorganic Compounds. Ketene is reported (68) to react with sulfuric acid to give acetylsulfoacetic acid (XVI) as a red viscous oil; presumably this compound is the effective catalyst in all the many reactions described in which sulfuric acid is used to catalyze reactions involving ketene.

$$H_2SO_4 + 2CH_2{:}C{:}O \longrightarrow CH_3CO_2SO_2CH_2CO_2H$$
(XVI)

If ketene and sulfur trioxide are passed into a mixture of dioxane and ethylene dichloride maintained at about room temperature, sulfoacetic anhydride,

$$\underline{CH_2 \cdot CO_2 \cdot SO_2}$$

is formed (222). This product was not isolated as such but was identified by its reaction with aniline to give anilinium sulfoacetanilide with some of the monoanilinium salt of sulfoacetic acid.

Fuming nitric acid reacts with ketene at −20 to −40° in anhydrous solvents such as methylene dichloride to give acetyl nitrate in good yield (211). In the absence of solvent, however, and at about 0°, ketene and fuming nitric acid combine to give tetranitromethane in 90% yield (56). It is believed that the reaction proceeds via the formation of nitroacetic acids with ultimate loss of carbon dioxide. The over-all equation is

$$4CH_2{:}C{:}O + 4HNO_3 \longrightarrow C(NO_2)_4 + CO_2 + 3CH_3CO_2H$$

Phosphoric acid (85%) may be converted with ketene to monoacetyl phosphate (17); the reaction is carried out near 0° in ether.

2. Reactions with Organometallic Compounds. Hurd, Sweet, and Thomas (139) first attempted the reaction between ketene and Grignard reagents and found it to proceed with violence to give a complex product. More recently, however, Dashkewich (58) has shown that the controlled reaction of ketene with ethylmagnesium chloride gives a 36-37% yield of ethyl methyl ketone; the use of ethylmagnesium bromide, however, gave appreciable amounts of diketene. Phenylmagnesium bromide and ketene give acetophenone (30–35%).

Diethylzinc in toluene with ketene at −80° gives ethyl methyl ketone (43%); similarly, the reaction with dimethylzinc gives acetone (39%). The use of diethylmagnesium, however, failed to give any ethyl methyl ketone (141).

Mercury compounds of the type RHgCl and R_2Hg react with ketene to give substituted methyl ketones, e.g., 2-furyl methyl ketone, 2,5-diacetylfuran, and acetophenone (81). Yields in general in these reactions are only 20–30% (49).

3. Reaction with Diazomethane. Ketene reacts with diazomethane to give cyclopropanone which is isolated as a hydrate in the presence of water or as the hemiacetal in alcohol. In water-free media a further molecule of diazomethane may combine to give cyclobutanone by ring enlargement (149,172,173). Labeled cyclobutanone has been made from $C^{14}H_2N_2$ (218).

4. Addition to —C=C—, —C=N—, and —N=N— Linkages. The addition of ketene to an olefinic double bond is a rarity. Brooks

and Wilbert (37) heated ketene with cyclopentadiene in toluene for 1 hr. at 100° and obtained a product which was either XVII or XVIII. Hydrogenation gave bicyclo[3.2.0]heptan-7-one which on oxidation with nitric acid gave glutaric acid.

(XVII) (XVIII)

Blomquist and Kwiatik (25) confirmed the earlier findings and successfully applied the reaction to cyclohexadiene. Recent work by Vogel and Müller (248a) has shown that the product obtained by Brooks and Wilbert was indeed XVII; they also found that butadiene combined with ketene to give a small yield of 3-vinylcyclobutanone.

In the following group of reactions ketene is treated with compounds having the system —N=C—C—. Since, however, these compounds appear to react in the enamine form, —N—C=C—, the reactions may appropriately be considered here as additions to an olefinic double bond. The reaction of Schiff's bases with ketene has been described in the patent literature (123); 1-methyl-4-(*N*-phenylimino)pentane, from aniline and methyl isobutyl ketone, on treatment with ketene, either without catalyst or in the presence of aluminum trichloride, zinc chloride, or boron trifluoride, affords an intermediate (XIX) which, on hydrolysis, gives 6-methylheptane-2,4-dione (XX). Similarly, acetophenone was converted through its Schiff's base with an aliphatic primary amine such as 2-amino-4-methylpentane to benzoylacetone. It would appear that this reaction would repay further study.

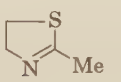
$$CH_3COCH_2CHMe_2 \longrightarrow CH_3C(:NPh)CH_2CHMe_2 \xrightarrow{CH_2:C:O}$$

$$CH_3COCH_2C(:NPh)CH_2CHMe_2 \xrightarrow{H_2O/H^+} CH_3COCH_2COCH_2CHMe_2$$

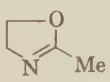
(XIX) (XX)

Quadbeck (209) has commented that compounds having the system —N=C—C— react with ketene only if they are capable of rearrangement to —N—C=C—. Thus, α-picoline, 2-methylquinoline, and 2-methylthiazole, in which the —N=C— double bond is part of an aromatic system, fail to react, whereas 2-methylthiazoline (XXI) and 2-methyloxazoline (XXII) react readily to give 2-acetonyl

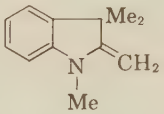
derivatives. Further, 2-methylene-1,3,3-trimethylindoline (XXIII), in which the —N—C=C— system present is incapable of rearranging to an imine form, reacts smoothly with ketene at 70–90° to give 2-acetonylidene-1,3,3-trimethylindoline (51).



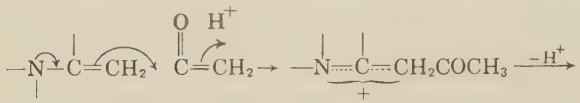
(XXI)



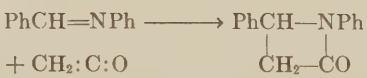
(XXII)



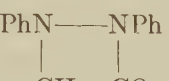
(XXIII)



Staudinger (230), in an early paper, showed that the general reaction of ketenes with compounds possessing an activated —C=N— double bond, such as benzylideneaniline, to give β-lactams, could be extended to the simplest member of the series. The reaction has recently been restudied by Pfleger and Jäger (200) who showed that the addition of ketene to ArCH:NAr, carried out at 180–200°, is hindered by substitution in either ring by *o*- or *p*-chloro and *o*-, *m*-, or *p*-nitro groups but favored by *m*-chloro and *p*-dimethylamino substitution.



Addition to a —N=N— double bond has recently been recorded by Schenck and Engelhard (216) who treated *cis*-azobenzene in hexane with ketene at 15° with simultaneous irradiation to give XXIV.



(XXIV)

5. C-Acetylation. The reaction of ketene with aromatic compounds in the Friedel-Crafts reaction has been studied by many workers with universally poor results. Ploeg (202) failed to obtain any product from the reaction of ketene with benzene in the presence of aluminum trichloride but obtained a small yield of acetyl compound from veratrole. Packendorff *et al.* (193) used an excess of aluminum trichloride and obtained a small yield of acetophenone; Williams and Osborn (254) noted that the purity of the ketene was important and reported a 32.7% yield of acetophenone in carbon disulfide with similar yields for the acylation of other aromatic hydrocarbons.

The *C*-acylation of acetylacetone with ketene has been accomplished (65); the presence of peroxide catalysts is claimed to give improved yields (177). Ketene was passed into a solution of acetylacetone in benzene at 30–40° containing benzoyl peroxide to give Ac_3CH in 80% yield. Boese has employed magnesium as a catalyst for the *C*-acylation of ethyl acetoacetate (30; see Section II-H).

III. Reactions of Isopropenyl Acetate

A. REACTIONS WITH HYDROXYL GROUPS

1. Acetylation. Isopropenyl acetate, prepared by the reaction of ketene with acetone (see Section II-H), may be used as a most convenient mild acetylating agent, being particularly useful for the acetylation of hydroxy compounds with a tendency to dehydrate, such as tertiary alcohols and α- and β-hydroxy esters and nitriles.

$$ROH + CH_2{:}CMeO_2CCH_3 \longrightarrow RO_2CCH_3 + CH_3COCH_3$$

The acetylation is normally catalyzed with sulfuric acid or *p*-toluene sulfonic acid, and the course of the reaction may readily be followed by allowing the acetone to distill from the reaction mixture as formed (118).

The acetylation of phosphoric acid with isopropenyl acetate has been studied (229).

2. Acetal Formation. In the presence of red mercuric oxide–boron trifluoride etherate, the reaction of isopropenyl acetate with alcohols takes a different course, giving the ketal of acetone with the alcohol employed (55).

$$2ROH + CH_2{:}CMeO_2CCH_3 \xrightarrow{BF_3/Hg^{2+}} (CH_3)_2C(OR)_2 + CH_3CO_2H$$

Recently it has been shown (124) that the mercuric oxide may with advantage be replaced by mercuric acetate, giving a smooth reaction free of inhibition period, and higher yields, e.g., diethyl ketal (70%), dibutyl ketal (83%).

B. REACTIONS WITH AMINES

Acetylation of aliphatic amines with isopropenyl acetate may generally be accomplished simply by refluxing the reactants without catalyst (118);

$$RR'NH + CH_2{:}CMeO_2CCH_3 \longrightarrow RR'NCOCH_3 + CH_3COCH_3$$

for weakly basic amines, e.g., aromatic amines, a catalytic quantity of sulfuric acid may be added (247). Isopropenyl acetate has been used for the acetylation of imidazole (34); a catalytic quantity of sulfuric acid is required.

C. ENOL ACETYLATION OF ALDEHYDES AND KETONES

A particularly useful application of isopropenyl acetate is as a reagent for the acetylation of enolizable aldehydes and ketones.

$$RCH_2COR' + CH_2{:}CMeO_2CCH_3 \rightleftharpoons RCH{:}CR'O_2CCH_3 + CH_3COCH_3$$

For the acetylation of higher boiling materials, the reagents may be heated in the presence of an acid catalyst, e.g., *p*-toluenesulfonic acid or sulfuric acid (0.4–1.0%), and the liberated acetone may be distilled continuously from the reaction mixture to give a substantially complete conversion of the original carbonyl compound. The reaction is a reversible one, and if, as is the case for lower boiling aldehydes, the acetone may not be separated as formed, an equilibrium mixture is formed (118,210).

Unsaturated aldehydes and ketones may be converted into enol acetates by the above procedure; crotonaldehyde gives a 95% yield of 1-acetoxy-1,3-butadiene. Diacetyl and acetylacetone give mixtures of mono- and dienol acetates. Ethyl acetoacetate and ethyl levulinate, on treatment with isopropenyl acetate, give good yields of the mixture of isomeric enol acetates already noted in Section II-H (118). Isopropenyl acetate has frequently been used for enol acetylation in the steroid field; as an example, the use by Moffett and Weisblat (179) for the enol acetylation of 20-ketosteroids in the

presence of *p*-toluenesulfonic acid may be quoted. The composition of the mixtures formed by the enol acetylation of ketones of the type $MeCOCH_2R$ has been studied (175).

D. REACTIONS WITH CARBOXYLIC ACIDS AND ANHYDRIDES

Carboxylic acids react smoothly with isopropenyl acetate in the presence of sulfuric acid to give a mixed anhydride and acetone:

$$RCO_2H + CH_2{:}CMeO_2CCH_3 \xrightarrow{H^+} RCO_2COCH_3 + CH_3COCH_3$$

If the acetone formed is removed at low temperature, the mixed anhydride may be isolated. Distillation of the reaction product at ordinary pressures results in disproportionation to a mixture of two acid anhydrides (118).

In the presence of mercuric ions, isopropenyl acetate undergoes acidolysis with carboxylic acids to give isopropenyl esters (67):

$$RCO_2H + CH_2{:}CMeO_2CCH_2 \overset{Hg^{2+}}{\rightleftharpoons} CH_2{:}CMeO_2CR + CH_3CO_2H$$

The preferred catalyst is mercuric oxide or acetate with boron trifluoride.

An exchange reaction between isopropenyl acetate and carboxylic acid anhydrides has been reported (201) to take place at 115–120° in the presence of sulfuric acid:

$$RCO_2COR + CH_2{:}CMeO_2CCH_3 \overset{H^+}{\rightleftharpoons} RCO_2COCH_3 + CH_2{:}CMeO_2CR$$

The mixed anhydride illustrated in the equation is thermally disproportionated, as already described, under the reaction conditions used.

E. MISCELLANEOUS REACTIONS

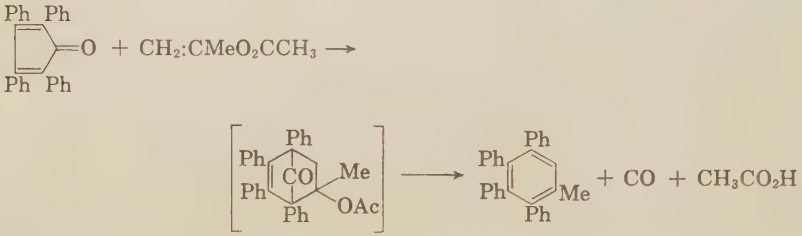
Isopropenyl acetate reacts with halogen acids (HI, HBr, and HCl) in ether to give the acetyl halide and acetone (118). Bromine and chlorine both add smoothly to the olefinic linkage in isopropenyl acetate to give α,β-dihalogen isopropyl acetates (248).

$$CH_2{:}CMeO_2CCH_3 + X_2 \longrightarrow XCH_2CXMeO_2CCH_3$$

The thermal rearrangement of isopropenyl acetate affords an excellent route to acetylacetone and is carried out in the vapor phase

in the absence of a catalyst at 400–450° (33); the use of homologs of isopropenyl acetate provides a general route to 1,3-diketones. The by-products (ketene, acetone, methylacetylene, acetic acid, etc.) and mechanism of this reaction have recently been studied (3).

The remarkable conversion by ring enlargement of 2,3,4,5-tetraphenylcyclopentadienone to 2,3,4,5-tetraphenyl-6-methylbenzene by treatment with isopropenyl acetate is noteworthy (1).



Treatment of enol esters with aqueous mercuric acetate followed by addition of potassium chloride gives chloromercury ketones; isopropenyl acetate itself gives $ClHgCH_2COCH_3$ (190).

IV. Reactions of β-Propiolactone

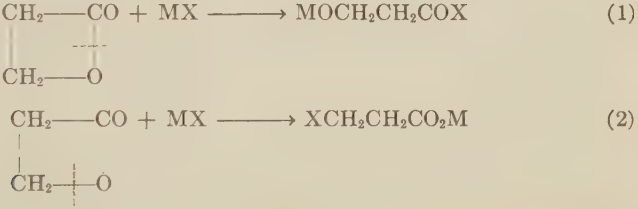
A. POLYMERIZATION

β-Lactones polymerize readily on heating, and this tendency makes it difficult to isolate by distillation the products arising from the reaction of ketene with higher aldehydes and ketones. The polymerization of β-propiolactone itself is catalyzed by acids, alkali, ferric chloride, etc., and the products so formed have been identified as polyesters which can be hydrolyzed to hydroacrylic acid and converted with ethanol in the presence of sulfuric acid to ethyl 3-hydroxypropionate. Pyrolysis of the polymer gives acrylic acid (83). This reaction is general and has been used to give a variety of β-substituted acrylic acids (29). The action of heat on monomeric β-lactones of low molecular weight, which polymerize readily, gives rise to a mixture of unsaturated acid, arising from pyrolysis of poly-

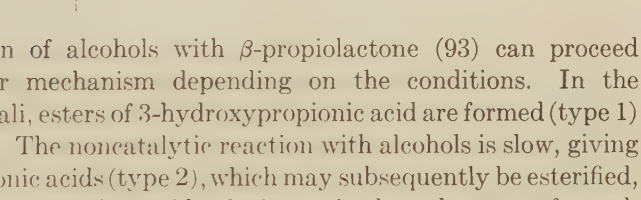
mer, and olefin plus carbon dioxide from residual monomer. The action of heat on higher molecular weight β-lactones such as those arising from diketones and ketoesters gives olefins, as has already been noted (Section II-I). The lactones from α,β-unsaturated aldehydes readily polymerize and give unsaturated acids on pyrolysis. The product from ketene and crotonaldehyde gives sorbic acid on treatment with sulfuric acid (31) or pyrolysis (103).

B. REACTIONS WITH HYDROXYL GROUPS, ETC.

The extensive work of Gresham and his colleagues has shown that β-propiolactone may react with a reagent MX (where M^+X^- indicates the normal polarities of the component parts of the reagent) according to two schemes



$$\begin{array}{l} CH_2\text{——}CO \\ \quad\vdots\quad\vdots \\ CH_2\text{——}O \end{array} + MX \longrightarrow MOCH_2CH_2COX \qquad (1)$$



$$\begin{array}{l} CH_2\text{——}CO \\ \quad\vdots\quad\vdots \\ CH_2\text{——}O \end{array} + MX \longrightarrow XCH_2CH_2CO_2M \qquad (2)$$

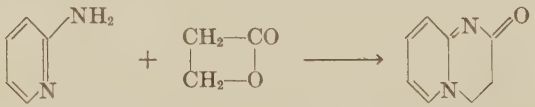
The reaction of alcohols with β-propiolactone (93) can proceed through either mechanism depending on the conditions. In the presence of alkali, esters of 3-hydroxypropionic acid are formed (type 1) in good yield. The noncatalytic reaction with alcohols is slow, giving 3-alkoxypropionic acids (type 2), which may subsequently be esterified, and polymer. In weakly acid solution, mixed products are formed, but, with higher concentration of acid, good yields of acrylic esters are obtained (219).

Phenol reacts slowly with β-propiolactone at room temperature to give 3-phenoxypropionic acid plus polymer. This reaction is also that which occurs in the presence of alkali (82). In the presence of sulfuric acid, however, phenyl 3-hydroxypropionate is exclusively formed in fair yield (88). Thiols readily react in the cold with β-propiolactone in aqueous alkali to give good yields of 3-alkylthiopropionic acids (95); ammonium dithiocarbamate and thiourea (84,96) give $NH_2CS_2CH_2CH_2CO_2NH_4$ and $NH_2C(:NH)SCH_2CH_2CO_2H$, respectively. In aqueous or alcoholic alkali, β-propiolactone reacts with the reactive methylene group of such compounds as

β-ketoesters, β-diketones, cyanoacetamide, and diethyl malonate to give 3-substituted propionic acids (16,90).

C. REACTIONS WITH AMINES

The reaction of amines with β-propiolactone may proceed either according to type 1 (to give hydroxyamides) or type 2 (to give amino acids) according to the conditions. Generally, aromatic amines give high yields of amino acids (89); only *p*-toluidine, of a wide range of substituted anilines studied by Hurd and Hayao (135), gave substantial amounts of hydroxyamide, although addition of type 1 has also been observed in other cases (89,146). With aliphatic amines and ammonia the orientation of addition is more complex and depends on the solvent used and the order of addition of the reactants (89,97,98). Ammonia in water with β-propiolactone gives mainly hydracrylamide, whereas, if the reaction is conducted in acetonitrile, β-alanine is obtained in good yield. Few correlations can be drawn. Dimethylamine on addition to an ether solution of β-propiolactone gives mainly the amino acid, whereas reversal of the order of addition gives the hydracrylamide (89). Replacement of dimethylamine with diethylamine gives *N*,*N*-diethylhydroacrylamide irrespective of the order of addition (89,98). With *tert*-amines, β-propiolactone gives betaines, $R_3\overset{+}{N}CH_2CH_2CO_2^-$ (76,89); pyridine reacts similarly. Hurd and Hayao (136) have shown that, whereas 2-aminopyridine and 2-aminothioazole normally give betaines, dihydropyrimidones are formed if the reaction is conducted in hot dilute hydrochloric acid, e.g.,



D. REACTIONS WITH ALKALI METAL SALTS

The reaction of β-propiolactone with alkali metal salts has been extensively studied and proceeds consistently through mechanism 2. Thus, sodium chloride reacts in aqueous solution to give sodium 3-chloropropionate (92). The further reaction of the lactone with the product can lead to $ClCH_2CH_2CO_2CH_2CH_2CO_2Na$ and higher condensation products; this tendency can be minimized by the use of a large excess of sodium chloride and by adding hydrogen

chloride. The reactions of β-propiolactone with other alkali metal halides, sodium hydrogen sulfide, sodium sulfide, ammonium sulfite, sodium thiosulfate (92), sodium dithionite, thiocyanate, nitrite, cyanide, arylsulfinates (91), acetate (85), etc., have all been examined and provide valuable routes to the appropriately 3-substituted propionic acids. The kinetics of the reaction of β-propiolactone with many of the anions represented above have been studied (13).

E. MISCELLANEOUS REACTIONS

Halogen acids react in aqueous or organic media to give good yields of 3-halogenopropionic acids (86,99,100), and aliphatic acids (86), in in the presence of sulfuric acid, add to β-propiolactone in the same sense (type 2 reaction). Acid halides and anhydrides, however, appear to react by type 1 cleavage, e.g., acetyl chloride gives 3-acetylpropionyl chloride, the reaction requiring catalysis with sulfuric acid. Phosphorus pentachloride and thionyl chloride give 3-chloropropionyl chloride (86).

Phenylmagnesium bromide and β-propiolactone react to give a mixture of chiefly 3-bromopropionic acid (type 2 addition) and some phenyl vinyl ketone (type 1 addition); methylmagnesium iodide behaves similarly. Polymerization is a competing side reaction in these instances (87).

β-Propiolactone undergoes a Friedel-Crafts reaction in the presence of aluminum trichloride with benzene to give mainly 3-phenylpropionic acid and some phenyl vinyl ketone; the reaction with anisole and toluene similarly indicated the incidence of both type 1 and type 2 addition, although with chlorobenzene only the aryl vinyl ketone was obtained (220). β-Propiolactone has been observed to alkylate (i.e., type 2 reaction) pyrrole (122) in the 2-position and indole in the 3-position (121,122).

Among other interesting reactions of β-propiolactone should be listed its use as a dieneophile (in place of acrylic acid) in the Diels-Alder reaction (94), i.e.,

The reaction of β-propiolactone with tertiary amines to give betaines is paralleled by its reaction with dimethyl sulfide in nitromethane in

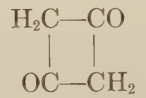
the presence of hydrogen chloride to give $Me_2\overset{+}{S}CH_2CH_2CO_2^-$ as the hydrochloride (22). Finally, hydrogenation in the presence of Raney nickel at 100–160° and 300–600 p.s.i. gives a high yield of propionic acid (115). The hydrogenation of other β-lactones or their polymers has been used as a convenient route to 3-substituted propionic acids (116).

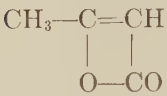
V. Reactions of Diketene

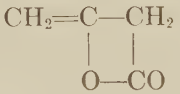
A. CONSTITUTION

The discoverers of diketene, Wilsmore and Chick (258), originally suggested that acetylketene (XXV) best represented the reactions of this substance, but, subsequently, from a further consideration of the physical and chemical properties of diketene, proposed the structure XXVI, cyclobutane-1,3-dione (259). Hurd and Williams (141) showed that ozonolysis of diketene gave pyruvic aldehyde and acetaldehyde and, on this evidence, suggested that diketene should be represented as a tautomeric equilibrium between acetylketene and XXVII. Important chemical evidence has since accumulated, however, which points to the structure XXVIII, a methylene β-propiolactone, as the correct one (26).

$CH_3COCH{=}C{=}O$ (XXV)


(XXVI)

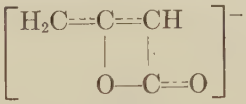

(XXVII)


(XXVIII)

The more important items of chemical evidence supporting this formulation include the early observation (259) that addition of bromine gives exclusively γ-bromoacetoacetyl bromide, the formation of which is inconsistent with formulas XXV and XXVII for diketene. Similarly, methanolysis with CH_3OD in carefully controlled experiments was shown to give $DCH_2COCH_2CO_2Me$ (148). Hydrogenation of diketene gives β-butyrolactone (see Section V-D-3), the formation of which is consistent with only XXVII or XXVIII. The generally

accepted structure (XXVIII) is further supported by the evidence afforded by allylic bromination experiments (see Section V-D-4) and by the more recent ozonolysis experiments of Hurd and Blanchard (129) who obtained formaldehyde and malonic acid in 30 and 15% yields, respectively. The chief product arising from the pyrolysis of diketene is ketene (26), but it is interesting to note that Fitzpatrick (78) showed that pyrolysis by means of an electrically heated Nichrome wire gave, in addition, a gas comprising carbon dioxide and allene in roughly equimolar amounts, consistent with cleavage of the diketene molecule where shown.

Infrared and ultraviolet absorption spectra (130,142,178,245), Raman spectra (240), electron diffraction measurements on diketene vapor (35), crystallographic studies (150), the proton magnetic resonance spectrum of liquid diketene at temperatures up to 120° (10), and the proton resonance absorption spectrum of crystalline diketene (79), give general support to structure XXVIII. An interesting aspect of the chemistry of this unique material is the observation of Wassermann (250) that diketene is a moderately strong acid (pK 7.1) which can be titrated in an aqueous medium. This feature may perhaps be explained by the considerable opportunities for resonance stabilization residing in the anion (XXIX).



(XXIX)

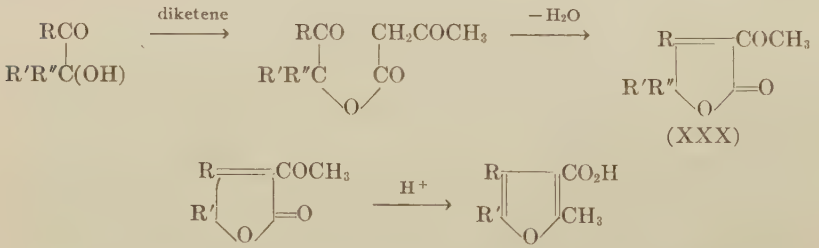
B. REACTIONS WITH HYDROXYL GROUPS

1. Reaction with Water. Diketene reacts smoothly with water at 50–100°C. in the presence of catalysts such as *p*-toluenesulfonic acid or *tert*-amines to give acetoacetic acid which decomposes to acetone and carbon dioxide (26,258). The reaction in the absence of catalysts is, however, slow; a freshly prepared mixture of diketene and water fails to give a color with ferric chloride, and diketene may

be distilled at atmospheric pressure as a constant boiling mixture with water with only 10% decomposition (26).

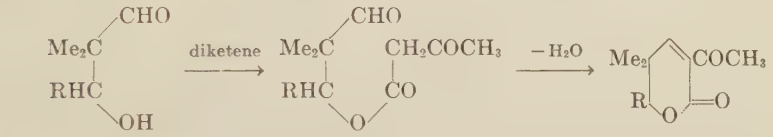
2. Reaction with Alcohols. The reaction of diketene with alcohols to give esters of acetoacetic acid is of general application. Wilsmore and Chick (258), who first observed this reaction, used sodium ethoxide in ethanol for the preparation of ethyl sodioacetoacetate (they appear to have misinterpreted the course of the reaction that took place (259)), and sodium alkoxides (0.5–1.0%) continue to be widely employed (152). Tertiary amines, particularly trimethylamine or triethylamine, are convenient catalysts (0.1–0.5%) and have been used for the acetoacetylation of a wide variety of alcohols (159, 161,162); it is not generally necessary to remove the amine from the reaction mixture before distillation of the ester. Acid catalysts, e.g., benzenesulfonic acid (26,259), have been used, but it is necessary to wash out the catalyst before isolation of the product.

The reaction of diketene with alcohols not only provides the preferred industrial route to the simple acetoacetic esters but also affords acetoacetic esters that are not normally obtainable by the conventional methods of Claisen condensation or ester exchange. These, in certain cases, are intermediates of interest for subsequent conversions. Thus, acyloins such as acetoin, propionoin, benzoin, etc., react readily with diketene to give acetoacetates which cyclize on being heated in the presence of triethylamine to give unsaturated lactones of formula XXX (159). These intermediates afford an interesting route to substituted furans; the lactones (XXX; R″ = H, R′ and R = alkyl or aryl) on treatment with a strong acid, such as hydrochloric acid in acetic acid, readily rearrange to β-furoic acids in good yields (160).

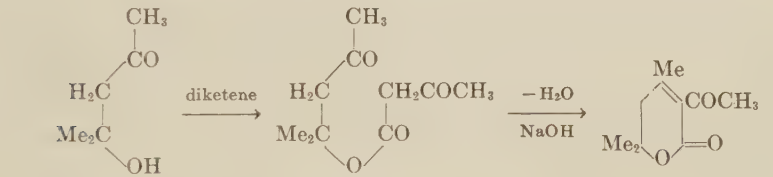


Aldols, which, by virtue of substitution on the α-carbon atom, may not be dehydrated to α,β-unsaturated aldehydes, react smoothly with

diketene to give acetoacetates, which readily cyclize in the presence of basic catalysts to give δ-lactones (XXXI). Diketene may be replaced by acetoacetic ester in the reactions described above with acyloins and aldols but with inferior yields. Diacetone alcohol, a tertiary alcohol, is readily acetoacetylated with diketene, and the acetoacetate may be converted to the lactone (XXXII) by treatment with aqueous alkali (159).

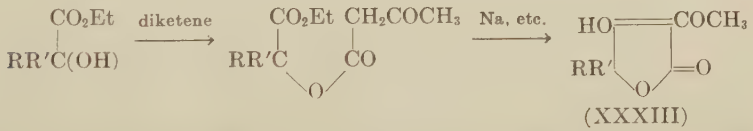


(R = H or $CHMe_2$) (XXXI)



(XXXII)

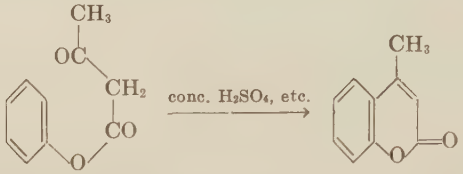
Hydroxy esters are readily acetoacetylated with diketene. The acetoacetates of α-hydroxy esters are of value in that they may be converted (162) by means of sodium or sodium alkoxides to α-acetyltetronic acids (XXXIII).



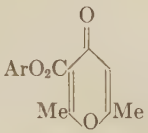
(XXXIII)

3. Reaction with Phenols. Phenols may be esterified with diketene in the presence of acid or, better, basic catalysts (166,196,197). Aryl acetoacetates, however, are generally unstable, the solid esters often liquefying with formation of the parent phenol within a few weeks. Distillation of aryl acetoacetates gives rise to extensive decomposition to dehydroacetic acid and the phenol; this cleavage appears to proceed particularly readily with phenols bearing strongly negative substituents. Thus, methyl salicylate on treatment with diketene in the presence of triethylamine at 60° gives dehydroacetic acid directly. Aryl acetoacetates, in many cases, cyclize on treat-

ment with sulfuric acid to give coumarins and, in general, give yields similar to those obtained from the respective phenol and ethyl acetoacetate in the Pechmann reaction. Particularly good yields of coumarins may be obtained from the acetoacetates of resorcinol (85%), pyrogallol (69%), *m*-cresol (75%), *p*-cresol (71%), 3,4-xylenol (87%), and α-naphthol (100%).



It had been earlier suggested that the Simonis reaction of phenols with β-ketoesters in the presence of phosphorus pentoxide to give chromones proceeded through the aryl acetoacetates; it was found, however, that the action of phosphorus pentoxide on these esters did not give chromones but afforded aryl 2,6-dimethyl-γ-pyrone-3-carboxylates (XXXIV) (166).



(XXXIV)

4. Pyrolysis of Unsaturated Alkyl Acetoacetates. The universal applicability of diketene for the production of alkyl acetoacetates has led to the intensive development of a field of particular importance in the synthesis of terpenes. Although in many of the reactions to be described, diketene may be replaced more or less successfully with ethyl acetoacetate, the chemistry of these reactions is so closely associated with that of diketene as to justify an account in this article.

In 1940 and 1941, Carroll (47) announced that the action of heat on mixtures of ethyl acetoacetate with certain α,β-unsaturated carbinols in the presence of a basic catalyst gave rise to the evolution of carbon dioxide and the formation of an unsaturated ketone. As examples may be quoted the conversion of cinnamyl alcohol to 3-phenyl-1-hexen-5-one (XXXV) and phenylvinylcarbinol to 1-phenyl-1-hexen-5-one (XXXVI).

$$PhCH{:}CHCH_2OH + CH_3COCH_2CO_2Et \longrightarrow$$

$$CH_3COCH_2CHPhCH{:}CH_2 + EtOH + CO_2$$
(XXXV)

$$PhCH(OH)CH{:}CH_2 + CH_3COCH_2CO_2Et \longrightarrow$$

$$PhCH{:}CHCH_2CH_2COCH_3 + EtOH + CO_2$$
(XXXVI)

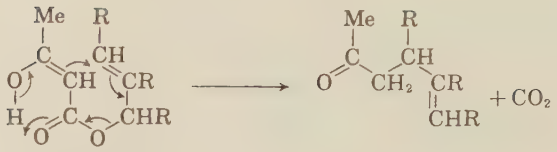
It was noted that the reactive methylene group of the acetoacetic ester had become linked to the allylic system which itself had become "inverted." Carroll suggested that the reaction was a type of Michael condensation, the α-carbon atom of the acetoacetic ester becoming linked to the vinyl group. Later, Kimel and Cope (152) systematically studied the reaction, which they considered to be the decarboxylation of the acetoacetates intermediately formed by transesterification; by using diketene, they were able to prepare a wide range of substituted allyl acetoacetates which they then subjected to pyrolysis. A summary of their results is given in Table II.

TABLE II
The Pyrolysis of Substituted Allyl Acetoacetates

Acetoacetate	Temp., °C.	Time, hr.	Ketone	Yield, %
Allyl[a]	185–200	92	Allylacetone	31
Methallyl[a]	200–215	25	Methallylacetone	26
Crotyl[a]	190–220	18	3-Methyl-1-hexen-5-one	37
Methylvinylcarbinyl	185–200	12	5-Hepten-2-one	80
Cinnamyl	250	1.2	3-Phenyl-1-hexen-5-one	74
Phenylvinylcarbinyl	200–240	1	1-Phenyl-1-hexen-5-one	88
Linalyl	170–235	1.2	Geranylacetone	78
Geranyl	220–230	8	Geranylacetone	23

[a] Ester heated in admixture with diphenyl ether.

The nature of the products obtained led the American workers to postulate a cyclic transition complex (XXXVII) to account for the allylic rearrangement observed.



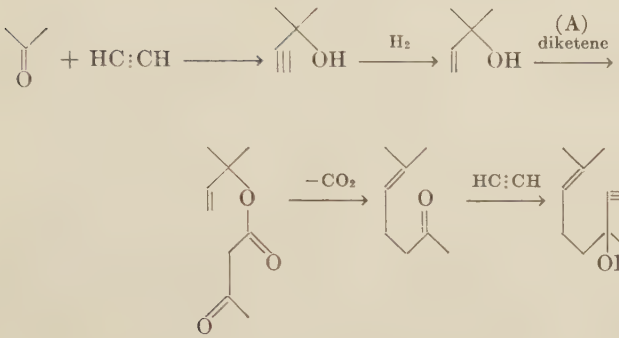
(XXXVII)

Examination of the yields afforded indicates that, in general, the *sec*-alkyl derivatives give higher yields of unsaturated ketones than the allylic isomers in which the hydroxyl is primary. Kimel (151) later showed that the pyrolysis of the tertiary ester, 2-methyl-3-buten-2-yl acetoacetate, gave 6-methyl-5-hepten-2-one, and, in a recent comprehensive paper, Kimel and his associates of the Technical Development Department of Hoffmann-La Roche Inc. (155) have reported the yields obtained on heating a wide range of tertiary esters of general formula XXXVIII. It was shown that insertion of

$$CMeR(O_2CCHR'''COCH_3)CR':CHR''$$
(XXXVIII)

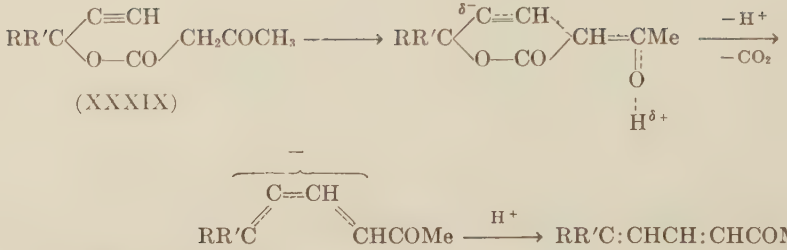
an alkyl group at R''' somewhat depressed the yield of ketone, and substitution at R'' markedly did so. The Hoffmann-La Roche workers have shown that the addition of aluminum alkoxides is of value in the pyrolysis of substituted allyl acetoacetates and gives rise to improved yields (155). Important contributions and extension of the reaction, both in the form originally studied by Carroll and as modified by Kimel and Cope, have been made by Naves (182), Teisseire (241–243), Dreux and Colonge (69), and Nazarov and his co-workers (186–189). Although the use of other β-ketoesters, such as acetone, dicarboxylic ester and ethyl 2-cyclopentanone-1-carboxylate, shows the general applicability of the reaction and greatly widens its scope, the value of diketene, where applicable, as an intermediate may be seen by comparison of the yield of methylheptenone obtained with ethyl acetoacetate (56%, 243) with that obtained with diketene as intermediate under the best conditions (83%, 154).

The type of reaction outlined has recently been used in an industrially applied synthesis of linaloöl starting from acetone, acetylene, and diketene as raw materials (154). The synthesis is outlined below; repetition of the cycle of operation A → B but starting with linaloöl gives nerolidol (186).



The observation that the pyrolysis of tertiary ethynylcarbinyl acetoacetates gives carbon dioxide and doubly unsaturated ketones was made independently by several workers (153,161,207). The decarboxylation of 2-methyl-3-butyn-2-yl acetoacetate (XXXIX; R = R′ = Me) to give 6-methyl-3,5-heptadien-2-one, the simplest instance of this reaction, takes place rapidly at 180–190° in the presence of *p*-toluenesulfonic acid or somewhat slowly in the absence of catalyst; yields of about 50% have been recorded (161,189). For the pyrolysis of esters of more complex carbinols such as dehydrolinaloöl, it is preferred to operate without catalyst (153,188,207,208) or in the presence of small quantities of acetic acid and aluminum isopropoxide, decalin being used as the reaction medium (155).

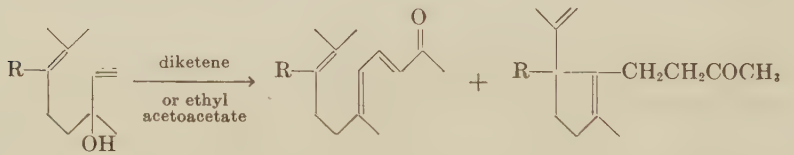
The reaction and the mechanism proposed by Lacey (161) are illustrated below. The scope of the reaction has been extensively explored, and it has been shown to be restricted to tertiary carbinols (an exception is the reported use of the phenylethynylcarbinyl ester (46)) in which the ethynyl hydrogen is unsubstituted; the acetoacetic ester may bear an α-substituent, but yields are lower. An important variant of the reaction for which superior yields are claimed in some instances is that described by Naves (183,184), Carroll (46), and Teissiere (241), in which the ethynylcarbinol is heated with ethyl acetoacetate to give the unsaturated ketone with the elimination of ethanol and carbon dioxide. The assertion (154) that this variation is identical in principle with that described above, the ethynylcarbinyl acetoacetate being an intermediate formed by ester exchange, is disputed (183). A comparison of the yields obtained by the two methods has been made (187).



(XXXIX)

Application of the above reaction to dehydrolinaloöl (XL; R = H), either by pyrolysis of the acetoacetate (153,154) or by heating with ethyl acetoacetate (183,188,207), gives a new and valuable synthesis of pseudoionone (XLI; R = H). The reaction is therefore of value in providing a route to the ionones, vitamin A, phytol, etc., independent of the availability of citral.

Replacement of 2-methyl-3-buten-2-ol in the synthesis of dehydrolinaloöl featured earlier with 2,3-dimethyl-3-buten-2-ol (e.g., from methyl isopropenyl ketone and methylmagnesium halide) affords a methyl-substituted dehydrolinaloöl (XL; R = Me) which, in turn, after treatment with diketene (153,155,188) or ethyl acetoacetate (184,188) gives pseudoirone (XLI; R = Me). A wide range of substituted pseudoionones has been prepared by the Hoffmann-La Roche team by means of these reactions (155).



(XL) (XLI) (XLII)

An interesting by-product of the pyrolysis of dehydrolinalyl acetoacetate or of a mixture of dehydrolinaloöl and ethyl acetoacetate is 4-(5-isopropenyl-2-methylcyclopenten-1-yl)-2-butanone (XLII; R = H). This side reaction, which may occur to the extent of 10–35%, has been observed to accompany the synthesis of the many pseudoionone homologs that have been made by this reaction (143,154,155, 185).

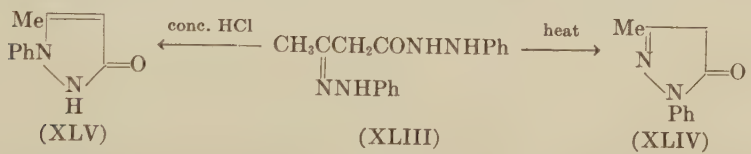
C. REACTIONS WITH AMINES, ETC.

The reaction of diketene with aniline to give acetoacetanilide was noted by Wilsmore and Chick (258,259), and the reaction affords a

method of industrial importance for the manufacture of acetoacetanilides in great variety for use as dyestuff or pigment intermediates. The condensation proceeds sufficiently rapidly in many cases, even with aromatic amines, for water to be used as reaction medium in which the amine may be dissolved or suspended; details have been given by Boese (26). Kinetic studies have shown that there is a rough parallel between the rate of the reaction and the dissociation constant of the amine (174). For the acetoacetylation of very weak bases, such as diphenylamine, *m*-nitroaniline, or carbazole, the use of tertiary amines as catalysts has been described; Lacey and Connolly (168) have proposed the use of catalysts, such as trimethylamine, and inert solvents, such as toluene, for the acetoacetylation of amines of dissociation constant less than 9×10^{-11}. Perekalin and coworkers (195,198) have used pyridine to catalyze reactions of this type and have successfully acetoacetylated indole (cf. ref. 121) and phthalimidine to the *N*-acyl derivatives.

With pyrroles, diketene gives *C*-acyl derivatives (246). Pyrrole itself gives a 60% yield of 2-acetoacetylpyrrole and substituted pyrroles are attacked in a vacant 2- (or 5-) position. 2,5-Dimethylpyrrole gives the 3-acetoacetyl derivative.

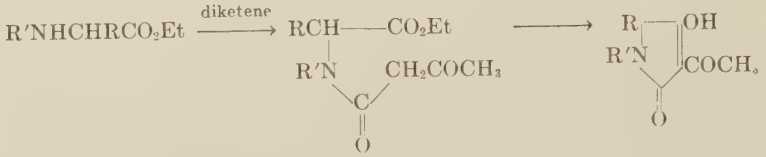
The reaction of diketene with two moles of phenylhydrazine gives as primary product the phenylhydrazide of acetoacetic acid phenylhydrazone (XLIII) (170,259). This, on heating, gives 1-phenyl-3-methyl-5-pyrazolone (XLIV); equimolar proportions of reactants in boiling benzene give XLIV directly in 79% yield. XLIII with strong hydrochloric acid gives a 92% yield of 1-phenyl-5-methyl-3-pyrazolone (XLV).



Petersen has shown that sulfonamides, e.g., $CH_3SO_2NH_2$ and $PhSO_2NH_2$, may be conveniently acetoacetylated with diketene in the presence of an equivalent of sodium hydroxide in aqueous tetrahydrofuran (199).

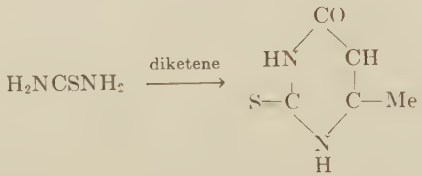
Amino acid esters react smoothly with diketene to give the expected acetoacetamides. The derivatives obtained from the esters of α-amino acids are of interest in that in the presence of a sodium

alkoxide they undergo an internal Claisen condensation to give α-acetyltetramic acids (XLVI). Similarly, methyl anthranilate may be acetoacetylated and cyclized to 3-acetyl-2,4-dihydroxyquinoline (165).

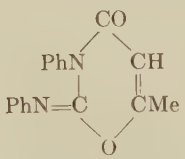


(XLVI)

Diketene reacts vigorously with thiourea in boiling acetic acid to give a 55% yield of 6-methyl-2-thiouracil; other thioureas react similarly (163).



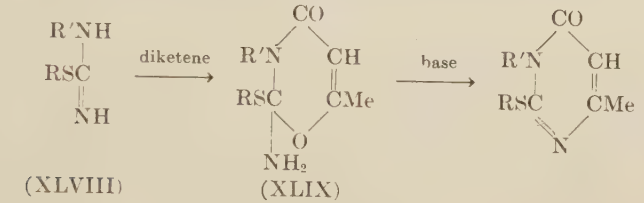
Boese treated urea with diketene in boiling dioxane to give a small yield of 6-methyluracil (27). Acetamidine, benzamidine, guanidine, and methylguanidine give the substituted pyrimidines expected from the analogy between diketene and acetoacetic ester. *N*,*N*′-Diphenylguanidine, however, was anomalous and gave a high yield of a product shown to be a derivative (XLVII) of 1,3-oxazine, a ring system that is almost unknown in an uncondensed form. *S*-Alkylthioureas (XLVIII; R′ = H, Ph, or Me) readily react with diketene



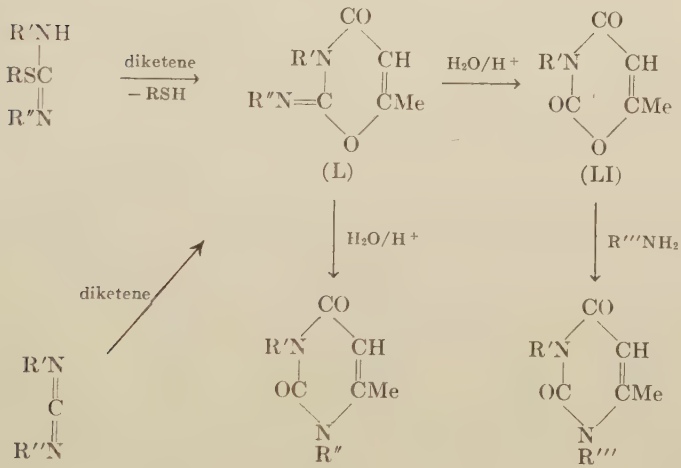
(XLVII)

but do not directly give the expected pyrimidones; the products were shown to be dihydro-1,3-oxazines (XLIX) which afford the expected pyrimidones on treatment with basic catalysts (163). *N*,*N*′-Disubstituted *S*-alkylthioureas also react smoothly with diketene, in this

case with the elimination of mercaptan, to give 2,3-dihydro-2-imino-4-oxo-1,3-oxazines (L), which may be hydrolyzed with acids to the 2,4-dioxo derivatives (LI); these compounds react with ammonia or primary amines to give pyrimidones (164). The reaction of carbodiimides with diketene also serves to give imino-1,3-oxazines (L) (169).



(XLVIII) (XLIX)



(L) (LI)

D. MISCELLANEOUS REACTIONS

1. Reaction with Thiols. Few references are available to the reaction of thiols with diketene; Theobald (244) has described the addition of ethanedithiol in the presence of α,α'-azobisisobutyronitrile and under the influence of ultraviolet light to give

$$(O{\cdot}CO{\cdot}CH_2{\cdot}CHCH_2SCH_2)_2$$

the mercaptan having added to the diketene methylene group in the anti-Markownikow sense.

2. Reaction with Carboxylic Acids. Hagemeyer has claimed that diketene reacts with aliphatic and aromatic carboxylic acids in the cold to give the acid anhydrides, acetone, and carbon dioxide (105). In the present writer's experience, diketene is virtually unaffected under such conditions. Some conversion, however, takes place in the presence of mineral acid catalysts as claimed by Hagemeyer, and in the process of isolation of the products from uncatalyzed experiments by distillation at atmospheric pressure. The reaction is, however, accompanied by resinification.

3. Hydrogenation. Although the hydrogenation of diketene to β-butyrolactone is invariably quoted as one of the most significant items of evidence to support the β-lactone type of formula for diketene, there is no account of the reaction with any experimental detail, other than in the patent literature. Wilsmore and Chick (259) found on hydrogenating diketene in ether with a platinum black catalyst that *n*-butyraldehyde was the main product. Hagemeyer (103,106) has claimed that if the hydrogenation is carried out at 60–70° and 300–500 p.s.i. in the presence of Raney nickel and with a diluent such as benzene, β-butyrolactone is produced; in the absence of diluents the diketene decomposed with violence. On increasing the temperature of hydrogenation to 120–150°, Hagemeyer obtained *n*-butyric acid. Aller (4,5) showed, however, that diketene, in either ethyl acetate or benzene and with either Raney nickel (well washed with a mixture of ethanol and acetic acid to remove traces of alkali that would otherwise lead to polymerization of diketene) or a nickel on kieselguhr catalyst, rapidly absorbed hydrogen at atmospheric pressure and room temperature to give an 85% yield of *n*-butyric acid; under no experimental conditions could β-butyrolactone be obtained with the catalysts named. Hydrogenation with a $Pd/BaSO_4$ catalyst in benzene at temperatures up to 75°, however, gave an 85% yield of product which was 92% β-butyrolactone and 8% *n*-butyric acid; the absorption of hydrogen ceased sharply when approximately the theoretical amount had been taken up.

4. Reactions with Halogens, etc. Wilsmore and Chick (259) showed that bromine readily reacts with diketene to give γ-bromoacetoacetyl bromide which gives the expected ester and amide with ethanol and aniline, respectively. Hurd and Abernethy (128) have described the chlorination of diketene in carbon tetrachloride at 0°; on removal of solvent, γ-chloroacetoacetyl chloride is obtained as

an orange liquid which may be distilled only with extensive decomposition but which affords derivatives of γ-chloroacetoacetic acid. Boese (26) has suggested γ-chloroacetoacetyl chloride and the corresponding bromoacyl bromide as sources of pure chloroacetone and bromoacetone, respectively; the products so obtained are uncontaminated with the higher halogenated acetones normally obtained from acetone and halogens.

$$ClCH_2COCH_2COCl + H_2O \longrightarrow ClCH_2COCH_3 + CO_2 + HCl$$

The allylic bromination of diketene with *N*-bromosuccinimide has been accomplished (23); the product, presumed to be

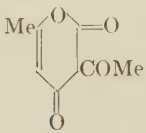
$$CH_2{:}\underline{C{\cdot}O{\cdot}CO{\cdot}CHBr}$$

was not isolated but was converted directly with ethanol to ethyl α-bromoacetoacetate in 43% over-all yield. In a similar series of experiments in which 2,4,*N*-trichloroaniline was used as the halogenating agent, ethyl α-chloroacetoacetate was obtained in a 35% yield.

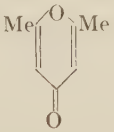
Diketene on treatment with anhydrous hydrogen chloride at a temperature that was progressively reduced from −7 to −50°, gave acetoacetyl chloride which has m.p. −50 to −51° but which decomposes to give dehydroacetic acid on being allowed to warm up to room temperature. Acetoacetyl chloride reacts with aniline to give acetoacetanilide (44% yield) and with ethanol to give ethyl acetoacetate (27% yield). With benzene in the presence of aluminum trichloride, acetoacetyl chloride gives benzoylacetone (27% yield), which is also obtained (12% yield) on treatment with phenylmagnesium bromide (137).

5. Formation of Dehydroacetic Acid. The dimerization of diketene at 80–90° to dehydroacetic acid (LII) was observed (258) soon after the first announcement of the discovery of diketene. The reaction is catalyzed by bases, and dehydroacetic acid is frequently encountered as a by-product in diketene reactions. Boese (28) has claimed the use of tertiary amines such as triethylamine and sodium alkoxides as catalysts and suggested that aromatic solvents be used as diluents at reaction temperature of 70–120°. In a detailed study, Boese *et al.* (32) found the reaction of diketene in boiling benzene to give dehydroacetic acid (54% yield), 2,6-dimethylpyrone (LIII, 4% yield),

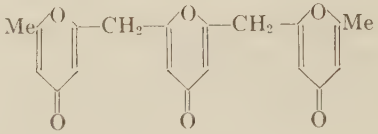
and a compound tentatively described as LIV (8% yield). Nordt (192) carried out the reaction in acetic anhydride in the presence of sodium acetate and has claimed an 80% yield of LII.



(LII)

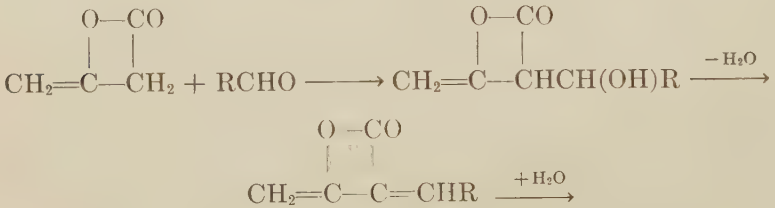


(LIII)

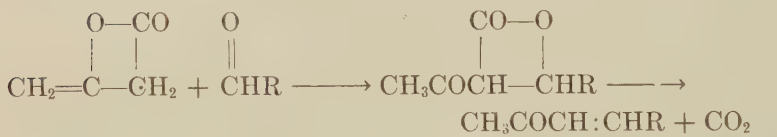


(LIV)

6. Reactions with Aldehydes and Ketones. Diketene reacts with aldehydes higher than formaldehyde to give α,β-unsaturated ketones. The reaction conditions used require the two reactants to be refluxed together, with or without diluent, for 24–48 hr. Boese (26) has proposed the mechanism illustrated in eq. 3, which involves a type of aldol condensation. Hagemeyer's representation (eq. 4), involving the well-known decarboxylation of a β-lactone, is perhaps more satisfying (103).

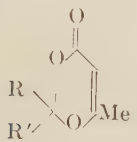


$$CH_3COC(:CHR)CO_2H \longrightarrow CH_3COCH{:}CHR + CO_2 \quad (3)$$



(4)

Diketene is substantially inert to ketones in the absence of catalysts; indeed, acetone is frequently used as a medium for the preparation of diketene from ketene. Carroll and Bader (48) have shown, however, that in the presence of acid catalysts, such as *p*-toluenesulfonic acid, diketene reacts smoothly and rapidly with ketones, such as acetone, ethyl methyl ketone, and acetophenone, to give adducts which have been formulated as 2,2-disubstituted derivatives of 4-methyl-6-oxo-1,3-dioxene-4 (LV).



(LV)

The acetone-diketene adduct, which may be obtained in 91% yield, is a stable liquid, which, since it gives many of the reactions of diketene itself, has been proposed as a stable source of diketene. The adduct gives dehydroacetic acid (51% yield) on being refluxed in toluene in the presence of calcium acetate, *n*-butyl acetoacetate (95% yield) with *n*-butanol in the presence of *p*-toluenesulfonic acid, and acetoacetanilide (45% yield) with aniline in xylene and in the presence of diethanolamine. The acid-catalyzed reaction between ketones and diketene has been observed by others (11) but was incorrectly described as leading to derivatives of isopropenyl acetoacetate (LVI).

$$CH_3COCH_2CO_2CMe{:}CH_2$$

(LVI)

7. C-Acylation. Diketene reacts readily with benzene (137) and xylenes (75) in the presence of aluminum trichloride to give benzoylacetone and derivatives. Boese (26) gives an account of a preparation of benzoylacetone by this method in 73% yield (cf. ref. 137). Diketene has also been reported to undergo the Friedel-Crafts reaction with aliphatic compounds; thus, with diisobutene in the presence of catalysts, such as sulfuric acid, zinc chloride, or boron trifluoride, diketene gives the 1,3-diketone $Me_3CCH_2CMe{:}CHCOCH_2COCH_3$ (38). A further interesting example of *C*-acylation is that of Fischer's base (XXIII), the *C*-acetylation of which with ketene has already been mentioned, to give 2-(acetylacetonylidene)-1,3,3-trimethylindoline (51).

References

1. Abramov, V. S., and A. P. Pakhamova, *J. Gen. Chem.* (*U.S.S.R.*), *24*, 1198 (1954); through *Chem. Abstr.*, *49*, 12419 (1955).
2. Agett, A. H., U. S. Pat. 2,421,976.
3. Allen, R. J. P., J. McGee, and P. D. Ritchie, *J. Chem. Soc.* (*London*), *1957*, 4700.
4. Aller, B. V., private communication.
5. Aller, B. V., Brit. Pat. 688,269.

6. van Alphen, J., *Rec. trav. chim.*, *43*, 823 (1924).
7. van Alphen, J., *Rec. trav. chim.*, *44*, 838 (1925).
8. d'Ans, J., and W. Frey, *Ber.*, *45*, 1845 (1912).
9. Ardis, A. E., and F. D. Stewart, U. S. Pats. 2,574,234, 2,574,235.
10. Bader, A. R., H. S. Gutowsky, G. A. Williams, and P. E. Yankwich, *J. Am. Chem. Soc.*, *78*, 2385 (1956).
11. Bal'yan, Kh. V., and A. L. Shtangeev, *J. Gen. Chem.* (*U.S.S.R.*), *24*, 238 (1954).
12. Barnett, B., U. S. Pat. 2,513,615.
13. Bartlett, P. D., and G. Small, *J. Am. Chem. Soc.*, *72*, 4867 (1950).
14. N. V. de Bataafsche Pet. Maat., Brit. Pat. 666,371.
15. N. V. de Bataafsche Pet. Maat., Brit. Pat. 670,130.
16. Beears, W. L., U. S. Pat. 2,600,387.
17. Bentley, R., *J. Am. Chem. Soc.*, *70*, 2183 (1948).
18. Bergmann, M., and F. Stern, *Ber.*, *63B*, 437 (1930).
19. Bergmann, M., and F. Stern, Ger. Pat. 453,577.
20. Berson, J. A., and W. M. Jones, *J. Am. Chem. Soc.*, *78*, 1625 (1956).
21. Bestian, H., *et al.*, *Ann.*, *566*, 210 (1949).
22. Blau, N. F., and C. G. Stuckwisch, *J. Am. Chem. Soc.*, *73*, 2355 (1951).
23. Blomquist, A. T., and F. H. Baldwin, *J. Am. Chem. Soc.*, *70*, 29 (1948).
24. Blomquist, A. T., R. W. Holley, and O. J. Sweeting, *J. Am. Chem. Soc.*, *69*, 2356 (1947).
25. Blomquist, A. T., and J. Kwiatik, *J. Am. Chem. Soc.*, *73*, 2098 (1951).
26. Boese, A. B., *Ind. Eng. Chem.*, *32*, 16 (1940).
27. Boese, A. B., U. S. Pat. 2,138,756.
28. Boese, A. B., U. S. Pat. 2,229,204.
29. Boese, A. B., U. S. Pat. 2,382,464.
30. Boese, A. B., U. S. Pat. 2,432,499.
31. Boese, A. B., U. S. Pat. 2,484,067.
32. Boese, A. B., A. B. Steele, and M. F. Dull, *J. Org. Chem.*, *14*, 460 (1949).
33. Boese, A. B., and F. G. Young, U. S. Pat. 2,395,800.
34. Boyer, J. H., *J. Am. Chem. Soc.*, *74*, 6274 (1952).
35. Bregman, J., and S. H. Bauer, *J. Am. Chem. Soc.*, *77*, 1955 (1955).
36. Brooks, R. E., U. S. Pat. 2,436,286; 2,449,447.
37. Brooks, B. T., and G. Wilbert, *J. Am. Chem. Soc.*, *63*, 870 (1941).
38. Byrns, A. C., U. S. Pat. 2,453,619.
39. Caldwell, J. R., U. S. Pat. 2,450,116.
40. Caldwell, J. R., U. S. Pat. 2,685,598.
41. Caldwell, J. R., U. S. Pats. 2,450,117, 2,450,118.
42. Caldwell, J. R., U. S. Pat. 2,487,849.
43. Caldwell, J. R., U. S. Pat. 2,585,223.
44. Caldwell, J. R., U. S. Pat. 2,739,158.
45. Carbide and Carbon Corp., Fr. Pat. 761,731.
46. Carroll, M. F., Brit. Pat. 762,656.
47. Carroll, M. F., *J. Chem. Soc.* (*London*), *1940*, 704, 1266; *1941*, 507.
48. Carroll, M. F., and A. R. Bader, *J. Am. Chem. Soc.*, *75*, 5400 (1953).
49. Chute, W. J., W. M. Orchard, and G. F. Wright, *J. Org. Chem.*, *6*, 157 (1941).

50. Clower, E. H., and F. E. Johnson, U. S. Pat. 2,697,115.
51. Coenen, M., *Ber.*, *80*, 546 (1947).
52. Coleman, G. H., R. L. Peterson, and G. E. Goheen, *J. Am. Chem. Soc.*, *58*, 1874 (1936).
53. Crouch, W. W., U. S. Pat. 2,509,483; through *Chem. Abstr.*, *44*, 10730 (1950).
54. Crouch, W. W., U. S. Pat. 2,639,293; through *Chem. Abstr.*, *48*, 3387 (1954).
55. Croxall, W. J., F. J. Glavis, and H. T. Neher, *J. Am. Chem. Soc.*, *70*, 2805 (1948).
56. Darzens, G., and G. Lévy, *Compt. rend.*, *229*, 1081 (1949).
57. Dashkewich, B. N., *Chem. Abstr.*, *37*, 4363 (1943).
58. Dashkewich, B. N., *J. Gen. Chem.* (*U.S.S.R.*), *8*, 779 (1938); *18*, 205 (1948); through *Chem. Abstr.*, *33*, 1293 (1939), and *42*, 7244 (1948), respectively.
59. Degering, E. F., U. S. Pat. 2,466,655.
60. Degering, E. F., and B. H. Gwynn, *J. Am. Chem. Soc.*, *64*, 2216 (1942).
61. Degering, E. F., and B. H. Gwynn, U. S. Pat. 2,383,965.
62. Degering, E. F., and B. H. Gwynn, U. S. Pat. 2,418,708.
63. Degering, E. F., and J. A. Spence, *J. Am. Chem. Soc.*, *66*, 1624 (1944); Brit. Pat. 605,471.
64. Degering, E. F., and J. A. Spence, U. S. Pat. 2,407,301.
65. Degering, E. F., and J. A. Spence, U. S. Pat. 2,417,381.
66. Degering, E. F., and J. A. Spence, U. S. Pat. 2,472,628.
67. Dickey, J. B., and T. E. Stanin, U. S. Pat. 2,646,437.
68. Doumani, T. F., and J. F. Cuneo, U. S. Pat. 2,411,823.
69. Dreux, J., and J. Colonge, *Bull. soc. chim. France*, *1955*, 1312.
70. Dunbar, R. E., and A. N. Bolstad, *J. Am. Chem. Soc.*, *77*, 4672 (1955).
71. Dunbar, R. E., and F. C. Garven, *J. Am. Chem. Soc.*, *77*, 4161 (1955).
72. Emery, A. R., and V. Gold, *J. Chem. Soc.* (*London*), *1950*, 1443.
73. Erickson, F. B., and E. J. Prill, *J. Org. Chem.*, *23*, 141 (1958).
74. Eschenbach, W., Ger. Pat. 638,441.
75. Estes, R. R., and A. Tockman, *Trans. Kentucky Acad. Sci.*, *13*, 265 (1952); through *Chem. Abstr.*, *47*, 6901 (1953).
76. Fiedorik, F. T., U. S. Pat. 2,548,428.
77. Fisher, G. T., A. F. MacLean, and A. W. Schnizer, *J. Org. Chem.*, *18*, 1055 (1953).
78. Fitzpatrick, J. T., *J. Am. Chem. Soc.*, *69*, 2236 (1947).
79. Ford, P. T., and R. E. Richards, *Discussions Faraday Soc.*, *19*, 193 (1955).
80. Geyer, B. G., and S. A. Ballard, U. S. Pat. 2,515,595.
81. Gilman, H., B. L. Woolley, and G. F. Wright, *J. Am. Chem. Soc.*, *55*, 2609 (1933).
82. Gresham, T. L., U. S. Pat. 2,449,991.
83. Gresham, T. L., J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, *70*, 998 (1948).
84. Gresham, T. L., J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, *70*, 1001 (1948).
85. Gresham, T. L., J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, *70*, 1003 (1948).
86. Gresham, T. L., J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, *72*, 72 (1950).

87. Gresham, T. L., J. E. Jansen, F. W. Shaver, and R. A. Bankert, *J. Am. Chem. Soc.*, *71*, 2807 (1949).
88. Gresham, T. L., J. E. Jansen, F. W. Shaver, R. A. Bankert, W. L. Becars, and M. G. Prendergast, *J. Am. Chem. Soc.*, *71*, 661 (1949).
89. Gresham, T. L., J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorik, *J. Am. Chem. Soc.*, *73*, 3168 (1951).
90. Gresham, T. L., J. E. Jansen, F. W. Shaver, M. R. Frederick, and W. L. Becars, *J. Am. Chem. Soc.*, *73*, 2345 (1951).
91. Gresham, T. L., J. E. Jansen, F. W. Shaver, M. R. Frederick, F. T. Fiedorik, R. A. Bankert, J. T. Gregory, and W. L. Beears, *J. Am. Chem. Soc.*, *74*, 1323 (1952).
92. Gresham, T. L., J. E. Jansen, F. W Shaver, and J. T. Gregory, *J. Am. Chem. Soc.*, *70*, 999 (1948).
93. Gresham, T. L., J. E. Jansen, F. W. Shaver, J. T. Gregory, and W. L. Beears, *J. Am. Chem. Soc.*, *70*, 1004 (1948).
94. Gresham, T. L., and J. E. Jansen, and F. X. Werber, *J. Am. Chem. Soc.*, *76*, 609 (1954).
95. Gresham, T. L., and F. W. Shaver, U. S. Pats. 2,449,992, 2,449,996.
96. Gresham, T. L., and F. W. Shaver, U. S. Pat. 2,478,838.
97. Gresham, T. L., and F. W. Shaver, U. S. Pats. 2,526,555, 2,526,556.
98. Gresham, T. L., and F. W. Shaver, U. S. Pat. 2,548,156.
99. Gresham, T. L., and F. W. Shaver, U. S. Pat. 2,422,728.
100. Gresham, T. L., and F. W. Shaver, U. S. Pat. 2,449,993.
101. Gresham, W. F., U. S. Pat. 2,449,471.
102. Grigsby, W. E., U. S. Pat. 2,443,451.
103. Hagemeyer, H. J., *Ind. Eng. Chem.*, *41*, 765 (1949).
104. Hagemeyer, H. J., U. S. Pat. 2,458,373; through *Chem. Abstr.*, *43*, 3836 (1949).
105. Hagemeyer, H. J., U. S. Pat. 2,476,859.
106. Hagemeyer, H. J., U. S. Pat. 2,484,498.
107. Hagemeyer, H. J., U. S. Pat. 2,476,860.
108. Hagemeyer, H. J., U. S. Pat. 2,469,110.
109. Hagemeyer, H. J., U. S. Pat. 2,450,134.
110. Hagemeyer, H. J., U. S. Pat. 2,466,420.
111. Hagemeyer, H. J., U. S. Pat. 2,450,133.
112. Hagemeyer, H. J., U. S. Pat. 2,496,791.
113. Hagemeyer, H. J., U. S. Pat. 2,478,388.
114. Hagemeyer, H. J., U. S. Pat. 2,484,499.
115. Hagemeyer, H. J., U. S. Pat. 2,484,500.
116. Hagemeyer, H. J., U. S. Pats. 2,484,497, 2,484,499.
117. Hagemeyer, H. J., and J. R. Caldwell, U. S. Pat. 2,462,357.
118. Hagemeyer, H. J., and D. C. Hull, *Ind. Eng. Chem.*, *41*, 2920 (1949).
119. Hamalainen, C., and J. D. Reid, *Ind. Eng. Chem.*, *41*, 1018 (1949).
120. Hanford, W. E., and J. C. Sauer, *Organic Reactions*, Vol. III, Wiley, New York, 1946, p. 108.
121. Harley-Mason, J., *Chem. and Ind. (London)*, *1951*, 886.
122. Harley-Mason, J., *J. Chem. Soc. (London)*, *1952*, 2433.

123. Haury, V. E., E. Cerrito, and S. A. Ballard, U. S. Pat. 2,418,173.
124. Hirsch, D. H., R. I. Hoaglin, and D. G. Kubler, *J. Org. Chem.*, *23*, 1083 (1958).
125. Hopff, H., and W. Rapp, U. S. Pat. 2,265,165.
126. Hull, D. C., and A. H. Agett, U. S. Pat. 2,422,679.
127. Hurd, C. D., *J. Am. Chem. Soc.*, *48*, 291 (1926).
128. Hurd, C. D., and J. L. Abernethy, *J. Am. Chem. Soc.*, *62*, 1147 (1940).
129. Hurd, C. D., and C. A. Blanchard, *J. Am. Chem. Soc.*, *72*, 1461 (1950).
130. Hurd, C. D., M. Calvin, and T. T. Magel, *J. Am. Chem. Soc.*, *63*, 2174 (1941)
131. Hurd, C. D., S. M. Cantor, and A. S. Roe, *J. Am. Chem. Soc.*, *61*, 426 (1939).
132. Hurd, C. D., and P. B. Cochran, *J. Am. Chem. Soc.*, *45*, 515 (1923).
133. Hurd, C. D., and M. F. Dull, *J. Am. Chem. Soc.*, *54*, 3427 (1932).
134. Hurd, C. D., O. E. Edwards, and J. R. Roach, *J. Am. Chem. Soc.*, *66*, 2013 (1944).
135. Hurd, C. D., and S. Hayao, *J. Am. Chem. Soc.*, *74*, 5889 (1952).
136. Hurd, C. D., and S. Hayao, *J. Am. Chem. Soc.*, *77*, 117 (1955).
137. Hurd, C. D., and C. D. Kelso, *J. Am. Chem. Soc.*, *62*, 1548 (1940).
138. Hurd, C. D., and A. S. Roe, *J. Am. Chem. Soc.*, *61*, 3355 (1939).
139. Hurd, C. D., A. D. Sweet, and C. L. Thomas, *J. Am. Chem. Soc.*, *55*, 335 (1933).
140. Hurd, C. D. and C. L. Thomas, *J. Am. Chem. Soc.*, *55*, 275 (1933).
141. Hurd, C. D., and J. W. Williams, *J. Am. Chem. Soc.*, *58*, 962 (1936).
142. Ikeda, Y., and T. Higashigaito, *Bull. Liberal Arts College, Wakayama Univ., Nat. Sci.*, *3*, 20 (1953); through *Chem. Abstr.*, *49*, 1579 (1955).
143. Isler, O., G. Saucy, L. H. Chopard-dit-Jean, W. Geux, and G. Ryser, *Helv. Chim. Acta*, *41*, 160 (1958).
144. Isoshima, T., *Bull. Inst. Chem. Research Kyoto Univ.*, *31*, 382 (1953).
145. Isoshima, T., and R. Nodzu, *Bull. Inst. Chem. Research Kyoto Univ.*, *32*, 139 (1954).
146. Iwakwa, Y., K. Nagakubo, H. Kawasumi, and S. Kigawa, *J. Chem. Soc. Japan*, *72*, 406 (1951); through *Chem. Abstr.*, *46*, 3013 (1952).
147. Johnson, F., and L. W. Newton, U. S. Pat. 2,395,930.
148. Johnson, J. R., and V. J. Shiner, *J. Am. Chem. Soc.*, *75*, 1350 (1953).
149. Kaarsemaker, S., and J. Coops, *Rec. trav. chim.*, *70*, 1033 (1951).
150. Katz, L., and W. N. Lipscomb, *Acta Cryst.*, *5*, 313 (1952); through *Chem. Abstr.*, *46*, 7394 (1952).
151. Kimel, W., U. S. Pat. 2,628,250.
152. Kimel, W., and A. C. Cope, *J. Am. Chem. Soc.*, *65*, 1992 (1943).
153. Kimel, W., and N. W. Sax, U. S. Pat. 2,661,368.
154. Kimel, W., N. W. Sax, S. Kaiser, G. G. Eichmann, G. O. Chase, and A. Offner, *J. Org. Chem.*, *23*, 153 (1958).
155. Kimel, W., J. D. Surmatis, J. Weber, G. O. Chase, N. W. Sax, and A. Offner, *J. Org. Chem.*, *22*, 1611 (1957).
156. Kuhn, R., and G. Quadbeck, *Ber.*, *84*, 844 (1951).
157. Küng, F. E., U. S. Pat. 2,356,459.
158. Lacey, R. N., Brit. Pat. 782,773.
159. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 816; Brit. Pat. 740,076 (with R. E. Graham).

160. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 822; Brit. Pat. 740,077.
161. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 827; Brit. Pat. 741,047.
162. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 832; Brit. Pats. 700,186, 737,458.
163. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 839; Brit. Pats. 699,583, 699,812.
164. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 845; Brit. Pat. 738,581.
165. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 850; Brit. Pat. 699,111.
166. Lacey, R. N., *J. Chem. Soc.* (*London*), *1954*, 854; Brit. Pat. 682,457.
167. Lacey, R. N., and A. E. Blades, Brit. Pat. 735,902.
168. Lacey, R. N., and E. E. Connolly, Brit. Pat. 715,896.
169. Lacey, R. N., and W. R. Ward, *J. Chem. Soc.* (*London*), *1958*, 2134.
170. Lecher, H. Z., R. P. Parker, and R. C. Conn, *J. Am. Chem. Soc.*, *66*, 1959 (1944).
171. Li, C., and A. Kalman, *J. Am. Chem. Soc.*, *68*, 285 (1946).
172. Lipp, P., J. Buchkremer, and H. Seeles, *Ann.*, *499*, 1 (1932).
173. Lipp, P., and R. Köster, *Ber.*, *64*, 2823 (1931).
174. Lyashenko, V. D., and T. A. Sokolova, *J. Gen. Chem.* (*U.S.S.R.*), *17*, 1868 (1947)
175. Mann, E. H., F. C. Frostick, and C. H. Hauser, *J. Am. Chem. Soc.*, *74*, 3228 (1952).
176. Mawer, F., U. S. Pat. 2,684,980.
177. Melstrom, D. S., and R. T. Hohn, U. S. Pat. 2,569,132.
178. Miller, F. A., and S. D. Kock, *J. Am. Chem. Soc.*, *70*, 1890 (1948).
179. Moffett, R. B., and D. I. Weisblat, *J. Am. Chem. Soc.*, *74*, 2183 (1952).
180. Morey, G. H., *Ind. Eng. Chem.*, *31*, 1129 (1939).
181. Mugdan, M., and J. Sixt, Brit. Pat. 498,280.
182. Naves, Y. R., Brit. Pat. 646,962.
183. Naves, Y. R., *Compt. rend.*, *240*, 1437 (1955).
184. Naves, Y. R., and P. Ardizio, *Bull. soc. chim. France*, *1955*, 1479; *1956*, 672.
185. Naves, Y. R., P. Ardizio, and B. Wolf, *Bull. soc. chim. France*, *1957*, 1213.
186. Nazarov, I. N., B. P. Gusev, and B. I. Gunar, *Izvest. Akad. Nauk C.C.C.P. Otdel Khim. Nauk*, *1957*, 1267.
187. Nazarov, I. N., S. M. Makin, V. B. Mochalin, I. I. Nazarova, V. P. Vinogradov, B. K. Kruptsov, O. A., Shavrygina, and D. V. Nazarov, *Doklady Akad. Nauk S.S.S.R.*, *114*, 1242 (1957).
188. Nazarov, I. N., L. A. Yanovskaya, B. P. Gusev, S. M. Makin, and I. I. Nazarova, *Doklady Akad. Nauk S.S.S.R.*, *114*, 1029 (1957).
189. Nazarov, I. N., L. A. Yanovskaya, B. P. Gusev, S. S. Yufit, V. I. Gunar, and V. A. Smit, *Doklady Akad. Nauk S.S.S.R.*, *114*, 331 (1957).
190. Nesmeyanov, A. N., I. F. Lutsenko, and Z. M. Tumanova, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, *1949*, 601; through *Chem. Abstr.*, *44*, 7225 (1950).
191. Neuberger, A., *Biochem. J.*, *32*, 1452 (1938).
192. Nordt, H., U. S. Pat. 2,729,652.
193. Packendorff, K., N. D. Zelinsky, and L. Leder-Packendorff, *Ber.*, *66B*, 1069 (1933).

194. Padgham, D. N., and J. B. Polya, *Australian J. Sci., 13,* 113 (1951); through *Chem. Abstr., 45,* 7006 (1951).
195. Perekalin, V. V., and O. M. Lerner, *J. Gen. Chem.(U.S.S.R.), 21,* 1995, 2219 (1951).
196. Perekalin, V. V., and K. B. Rall, *J. Gen. Chem. (U.S.S.R.), 25,* 259, 781 (1955); through *Chem. Abstr., 50,* 1794, 2521 (1956).
197. Perekalin, V. V., and K. B. Rall, *Zhur. Priklad. Khim., 25,* 1330 (1952); through *Chem. Abstr., 47,* 11155 (1953).
198. Perekalin, V. V., and N. M. Slavachevskaya, *J. Gen. Chem. (U.S.S.R.), 24,* 2164 (1954).
199. Petersen, S., *Ber., 83,* 551 (1950).
200. Pfleger, R., and A. Jäger, *Chem. Ber., 90,* 2460 (1957).
201. Phillips, B., U. S. Pats. 2,466,738; 2,568,296.
202. Ploeg, W., *Rec. trav. chim., 45,* 342 (1926).
203. Ponomarew, A. A., and Yu. B. Isaev, *J. Gen. Chem. (U.S.S.R.), 21,* 1045 (1951).
204. Ponomarew, A. A., and Yu. B. Isaev, *J. Gen. Chem. (U.S.S.R.), 20,* 1079 (1950).
205. Ponomarew, A. A., and Yu. B. Isaev, *J. Gen. Chem. (U.S.S.R.), 22,* 652 (1952); through *Chem. Abstr., 47,* 2695 (1953).
206. Porai-Koshits, B. A., L. S. Efros, and K. Y. Mar'yanovskaya, *J. Gen. Chem. (U.S.S.R.), 26,* 426 (1956).
207. Preobrazhenskiĭ, N. A., G. I. Somokhvalov, M. A. Miropol'skaya, *Doklady Akad. Nauk S.S.S.R., 107,* 103 (1956).
208. Preobrazhenskiĭ, N. A., G. I. Somokhvalov, M. A., Miropol'skaya, and L. D. Lukyanova, *J. Gen. Chem. (U.S.S.R.), 27,* 2501 (1957).
209. Quadbeck, G., *Angew Chem., 68,* 361 (1956).
210. Quattlebaum, W. M., and C. A. Noffsinger, Brit. Pats. 615,521, 615,522.
211. Reuter, M., Ger. Pat. 849,405.
212. Rice, F. O., and J. Greenberg, *J. Am. Chem. Soc., 56,* 2132 (1934).
213. Rice, F. O., J. Greenberg, C. E. Waters, and R. E. Vollrath, *J. Am. Chem. Soc., 56,* 1760 (1934).
214. Roe, A., and J. W. McGehee, *J. Am. Chem. Soc., 70,* 1662 (1948).
215. Roy, G. C., U. S. Pat. 2,396,201.
216. Schenck, G. O., and N. Engelhard, *Angew. Chem., 68,* 71 (1956).
217. Schnizer, A. W., U. S. Pat. 2,820,057.
218. Seminow, D. A., E. F. Cox, and J. D. Roberts, *J. Am. Chem. Soc., 78,* 3221 (1956).
219. Shaver, F. W., U. S. Pat. 2,510,423.
220. Shaver, F. W., U. S. Pat. 2,587,540.
221. Smirnova, N. V., A. P. Skoldnikov, and K. A. Kocheschov, *Doklady Akad. Nauk S.S.S.R., 84,* 737 (1952); through *Chem. Abstr., 47,* 3233 (1953).
222. Smith, C. W., U. S. Pat. 2,566,810.
223. Šorm, F., and J. Smrt, *Chem. listy, 48,* 217 (1954); through *Chem. Abstr., 49,* 2311 (1955).
224. Šorm, F., and J. Smrt, *Chem. listy. 47,* 413 (1953); through *Chem. Abstr., 49,* 175 (1955).

225. Šorm, F., J. Smrt, and J. Beránek, *Chem. listy, 49*, 573 (1955); through *Chem. Abstr., 50*, 2429 (1956).
226. Šorm, F., J. Smrt, and J. Beránek, *Chem. listy, 48*, 679 (1954); through *Chem. Abstr., 49*, 9545 (1955).
227. Šorm, F., J. Smrt, and J. Beránek, *Chem. listy, 49*, 73 (1955); through *Chem. Abstr., 49*, 15773 (1955).
228. Šorm, F., J. Smrt, J. Beránek, and J. Sicher, *Chem. listy, 49*, 78 (1955); through *Chem. Abstr., 49*, 15773 (1955).
229. Stadtman, E. R., and F. Lipmann, *J. Biol. Chem., 185*, 549 (1950).
230. Staudinger, H., *Ber., 50*, 1035 (1917).
231. Staudinger, H., *Die Ketene*, Ferdinand Enke, Stuttgart, 1912.
232. Staudinger, H., and H. W. Klever, *Ber., 41*, 594, 1516 (1908).
233. Staudinger, H. P., and K. H. W. Türck, Brit. Pat. 539,163.
234. Steadman, T. R., U. S. Pat. 2,424,589.
235. Steinkopf, W., and M. Kühnel, *Ber., 75B*, 1323 (1942).
236. Stern, K. G., and A. White, *J. Biol. Chem., 122*, 371 (1938).
237. Stewart, F. D., U. S. Pat. 2,596,826.
238. Svetkin, Y. V., *J. Gen. Chem.* (*U.S.S.R.*), *26*, 1216 (1956).
239. Svetkin, Y. V., and Y. N. Forostyan, *J. Gen. Chem.* (*U.S.S.R.*), *25*, 1966 (1955); through *Chem. Abstr., 50*, 8461 (1956).
240. Taufen, H. J., and M. J. Murray, *J. Am. Chem. Soc., 67*, 754 (1945).
241. Teisseire, P., *Recherches, 5*, 3 (1955).
242. Teisseire, P., *Recherches, 7*, 29 (1957).
243. Teisseire, P., P. Bernard, and B. Corbier, *Recherches, 6*, 30 (1956).
244. Theobald, C. W., U. S. Pat. 2,675,392.
245. Thompson, H. W., and D. W. Whiffen, *J. Chem. Soc.* (*London*), *1946*, 1005.
246. Treibs, A., and K. H. Michl, *Ann., 577*, 129 (1952).
247. Utermohlen, W. P., U. S. Pat. 2,472,633.
248. Utermohlen, W. P., U. S. Pat. 2,404,416.
248a. Vogel, E. and K. Müller, *Ann., 615*, 29 (1958).
249. Vollmann, H., F. Schoffler, and W. Ostrowski, Ger. Pat. 736,504.
250. Wassermann, A., *J. Chem. Soc.* (*London*), *1948*, 1323.
251. Williams, J. W., Y. J. Dickert, and J. A. Krynitsky, *J. Am. Chem. Soc., 63*, 2510 (1941).
252. Williams, J. W., and J. A. Krynitsky, *Organic Syntheses*, Vol. XXI, Wiley, New York, 1941, p. 13.
253. Williams, J. W., and J. A. Krynitsky, *Organic Syntheses*, Vol. XXI, Wiley, New York, 1941, p. 64.
254. Williams, J. W., and J. M. Osborn, *J. Am. Chem. Soc., 61*, 3438 (1939).
255. Williams, J. W., and A. Sadle, *J. Am. Chem. Soc., 62*, 2801 (1940).
256. Wilsmore, N. T. M., *J. Chem. Soc.* (*London*), *91–2*, 1938 (1907); Wilsmore, N. T. M., and A. W. Stewart, *Nature, 75*, 510 (1907).
257. Wilsmore, N. T. M., and F. Chick, *Proc. Chem. Soc.* (*London*), *24*, 77 (1908).
258. Wilsmore, N. T. M., and F. Chick, *J. Chem. Soc.* (*London*), *93–4*, 946 (1908).
259. Wilsmore, N. T. M., and F. Chick, *J. Chem. Soc.* (*London*), *97–8*, 1978 (1910).

260. Wilsmore, N. T. M., and S. Deakin, *J. Chem. Soc.* (*London*), *97–8*, 1968 (1910).
261. Wollenberg, O., *Ber.*, *67B*, 1675 (1934).
262. Young, F. G., U. S. Pat. 2,461,016.
263. Young, F. G., U. S. Pat. 2,511,423.
264. Young, F. G., *J. Am. Chem. Soc.*, *71*, 1346 (1949).
265. Young, F. G., and J. T. Fitzpatrick, U. S. Pat. 2,580,714.
266. Zaugg, H. E., *Organic Reactions*, Vol. VIII, Wiley, New York, pp. 305–63.

NUCLEAR MAGNETIC RESONANCE IN ORGANIC STRUCTURAL ELUCIDATION*

By HAROLD CONROY, *Yale University, New Haven, Conn.*

CONTENTS

I. Introduction 265
II. Basic Theory and Practice of NMR 268
III. The Chemical Shift 273
A. Shielding Constants 273
B. Standardization 274
C. Chemical Shift and Electronegativity 277
D. Chemical Shift and Magnetic Anisotropy 281
E. Standardized Values of Chemical Shift 287
IV. Spin-Coupling 291
A. Mechanism 291
B. Approximate Treatment 293
C. The High Resolution Hamiltonian 296
D. The Two-Proton System AB 301
E. The Three-Proton System AB_2 302
F. The Three-Proton Systems ABC and ABX 304
G. The Four-Proton Systems A_2B_2 and A_2X_2 305
H. Other Spin-Coupled Systems 307
I. Multiplet Moment Theorems 307
J. Correlation of Coupling Constant with Structure 308
V. Kinetic Effects 312
A. Proton Residence Times 312
B. Kinetics of Conformational Changes 312
VI. Applications to Structural Problems 314
References 325

I. Introduction

The first nuclear magnetic resonance (NMR) experiments were described in 1946 by Purcell, Torrey, and Pound (46) and by Bloch, Hansen, and Packard (47). The first concerted application to structural organic chemistry was reported by Meyer, Saika, and

* Contribution number 1528, Sterling Chemistry Laboratory, Yale University.

Gutowsky (3) in 1953. The growth of the technique in the several years since then has been remarkable. One might compare its evolution as an analytical tool to the quick and widespread development of the organic infrared technique over the past fifteen years; NMR captured the chemist's imagination straightaway, while those of us having become accustomed to the power and versatility of infrared must contemplate the newer method taking its place with the old. It would be idle to discuss NMR in terms of its displacement of infrared or other spectroscopic means. The methods are complementary: they give different kinds of information. Still, the NMR procedure has repeatedly been shown to yield the kind of structural evidence which can be obtained by ordinary chemical or physical means only with the greatest difficulty, if at all, so that we understand its striking rise in popularity even in the infancy of the technique.

Many of the theoretical aspects of NMR have been very comfortably apprehended, even if they are presently far from generally understood by chemists. The foundations were carefully laid by the physicists, the majority of whom promptly turned to other, presumably more satisfying, activities as soon as the chemical potentialities were becoming clear. From the chemical viewpoint there are only two exceptions to the general tendency of theory to keep pace with experiment in this field; these are the *a priori* calculation from structure of chemical shift and of spin-spin coupling parameters. The difficulties here are considerable, but the problem is far from hopeless and progress is beginning to be made.

The material included in this article has been carefully chosen from the point of view of practical utility to the organic chemist who is interested in solving structural problems with NMR. Some fields have been completely ignored, including the entire treatment of solid state spectra; emphasis is concentrated almost exclusively upon proton resonance, with very little mention of the extensive work with other nuclei of spin $^1/_2$ or those possessing quadrupole moments. The reason is plain: the high resolution proton magnetic resonance spectroscopy of liquids has thus far most clearly been shown to be generally applicable to the problems the organic chemist will encounter. Despite this practical outlook, the reader will find considerable space devoted to the theoretical, sometimes mathematical aspects. This is a result of the author's conviction that NMR in chemical usage is already far less empirical than, say, infrared, and

that the trend will be toward further reduction of such empiricism. Without doubt the intelligent use of NMR demands more of an understanding of the principles involved than does any other form of spectroscopy in popular organic use today. The physicists who developed this body of theory were careful that their conclusions and especially their methods would be intelligible—to other physicists—so that some considerable effort to bridge the gap might well be spent. We shall be content here to discuss only those results of the theory having direct structural analytical significance; a far more comprehensive treatment of the physical and mathematical facets of NMR is given in the excellent book by Andrew (5). Appropriate mention should be made of the review article by Wertz (54) and the recent monographs by Roberts (55), by Pople, Schneider, and Bernstein (117), and by Jackman (118).

An attractive feature of NMR spectroscopy is that the molecule as a whole is "transparent," so that one can examine without interference a selected single class of magnetic nuclei. The region of proton resonance will not contain any peaks due to any of the other atoms within the molecule because, even if these others are magnetic, their absorption lines will appear at displacements enormous compared to the range of the proton spectrum. The carbon and oxygen framework of the molecule produces no effect of its own at all. The presence of other magnetic nuclei (e.g., nitrogen, fluorine, phosphorus, deuterium) is occasionally reflected in the proton spectrum but only as a perturbation in peak position or multiplicity which is usually of a predictable character. Although magnetic, the other halogen nuclei (chlorine, bromine, and iodine) do not affect the multiplicity of the proton peaks since the electric field associated with the nuclear quadrupole moment interacts with the environment and causes the nuclear spin to flip so rapidly that its effect on neighboring protons averages to zero. NMR spectroscopy is therefore most commonly used in organic work when information is needed about the number of different kinds of hydrogen atoms in a molecule, and about the relationship of these to each other and to the other atoms present. As might be expected, the simplest spectra are usually those of compounds containing a small number of different kinds of hydrogen. Large molecules with low symmetry generally give rather complicated spectra, but even in this case valuable information can usually be extracted without the necessity of a complete analysis and assignment of all peaks.

II. Basic Theory and Practice of NMR

The concept of electron spin is well known. Many nuclei possess an intrinsic angular momentum or spin, which in analogy with that of the electron, is accompanied by a characteristic magnetic moment; one might imagine the magnetic moment to be generated by the rotation of the associated electric charge. When an electronic or nuclear magnetic dipole is placed in an external magnetic field, it is found that the dipole cannot continuously assume all directions; instead there is a discrete set of possible orientations and the system is said to be quantized. Since the potential energy of a dipole will depend upon its orientation with respect to the external field, the energy will be quantized as well and the system will be allowed only a set of discrete energies. Of course quantization on the atomic level is very familiar, and the consequences of its operation in connection with the motion of an electron in the electrostatic field of an atomic nucleus form the basis of chemistry itself.

The spin of a nucleus is characterized by a number, I, either zero or some integral multiple of $^1/_2$. We shall be concerned primarily with nuclei of spin $^1/_2$, particularly the proton; other nuclei of spin $^1/_2$ which have been studied by spin resonance techniques include F^{19}, P^{31}, and C^{13}. The common isotopes C^{12} and O^{16} are nonmagnetic ($I = 0$). A nucleus of spin $^1/_2$ will have one of two possible energy levels $\pm\mu H$ in an external magnetic field H, where μ is the component of the nuclear magnetic moment in the direction of H. These two levels correspond roughly to alignment of the nuclear moment with or against the magnetic field. The spin can be flipped; that is, a transition can be excited from one energy level to another, and this will be accompanied by the absorption or emission of a quantum of energy

$$\Delta E = h\nu = 2\mu H$$

where ν is the frequency of the electromagnetic radiation absorbed or emitted. For protons at 10^4 gauss magnetic field strength, the resonant frequency is in the convenient rf range of 40 Mc./sec. The resonant frequency is seen to be proportional to the strength of the applied field.

$$\nu = (2\mu/h)H = (\gamma/2\pi)H$$

where the gyromagnetic ratio,

$$\gamma = 4\pi\mu/h = (2\pi/h)(\mu/{}^1/_2) = \mu/\hbar I$$

is a fundamental nuclear constant.

Electromagnetic radiation theory shows that the probability of a transition from the lower state to the upper state by absorption is equal to the probability of transition downwards by radiation-induced emission (Einstein, 43). The probability of a transition downwards by spontaneous emission is negligible in the case of an isolated nucleus (44). If the numbers of nuclei in each energy level were equal, the rate of transitions up and down would be equal, and there would be no net absorption or emission. Actually, however, the nuclear spins interact with their surroundings; at equilibrium the population of the lower level exceeds that of the upper level by the Boltzmann factor, $\exp(2\mu H\ kT_s)$, where k is the Boltzmann constant and T_s is the "spin temperature." In the absence of applied radiation, the spin temperature tends to reach that of the surroundings. Under ordinary conditions, for protons in a field of 10^4 gauss, the Boltzmann factor is approximately $1 + 10^{-5}$; it is this exceedingly small but finite excess of population in the lower state which permits a net absorption of energy from the rf field and, therefore, makes the resonant frequency an experimentally measurable quantity.

The absorption of energy corresponds to the transfer of some of the excess population in the lower level to the upper level. If there were no interaction between the system of nuclear spins and the surroundings, called the "lattice," absorption could continue only until the populations were equal, when the spin temperature would reach infinity and absorption would cease. In a real physical system the various mechanisms of interaction with the lattice tend to cool the nuclear spins so that a steady-state results; the cooling process is called *spin-lattice relaxation*.

Consider a spin system at a temperature, T_s, different from the lattice temperature T, with the excess number n of nuclei per cubic centimeter in the lower state. The rate of approach to thermal equilibrium in the absence of the rf field will be

$$dn/dt = (1/T_1)(n_0 - n)$$

where n_0 is the value of n when the system is in thermal equilibrium with the lattice, and $1/T_1$ measures the degree of spin-lattice interaction. T_1, the spin-lattice relaxation time, is a characteristic time

constant for the exponential decay represented in the integrated expression

$$n = -(n_0 - n_a) \exp(-t/T_1) + n_0$$

where n_a is the initial value of n. When radiation is applied, another term must be added to account for the upward transitions which correspond to the net absorption of energy. Thus

$$dn/dt = (n_0 - n)/T_1 - 2nP$$

where P is the probability per unit time that a nucleus will undergo an induced transition between the two levels, and nP is the net probability of a transition upward (45). Each upward transition reduces n by 2. A steady state is reached when $dn/dt = 0$, and in this condition the steady state value, n_s, of the excess number is given by

$$n_s = n_0/(1 + 2PT_1)$$

The significance of this equation lies in the fact that the rate of absorption of energy and hence the intensity of the observed resonance line will be proportional to n_sP. The probability, P, depends on the square of the amplitude of the rf magnetic field, applied in a direction perpendicular to that of H. If a sufficiently strong rf field is applied, n_s/n_0 becomes quite small, and the system is said to be *saturated;* i.e., a point is reached beyond which any increase in the applied rf field causes very little increase in absorption. With a given moderately strong rf field, the saturation factor n_s/n_0 will depend upon T_1; the longer the relaxation time, the more readily saturation will be approached. T_1 is usually longer for solids than for liquids and gases; for liquids the time is in the order of 1 sec. The presence of paramagnetic ions in a liquid promotes the relaxation process and may reduce T_1 to less than 10^{-4} sec.

Different protons within the lattice, even within the same molecule, will have different values of T_1; they will therefore give absorption lines of different strength. Nonlinearity between absorption intensities and intrinsic transition probabilities is obviously to be avoided in structural work, especially if one uses the intensities as a means of assignment of group resonance lines. Common practice therefore involves the application of the weakest rf field consistent with the receiver limitations of sensitivity and signal to noise ratio,

the hope being that the spin systems will be as far removed from saturation as possible.

Most instruments employ rf excitation at constant frequency, and in order to scan the spectrum the applied magnetic field is varied over the desired range at a linear rate. The frequency stability of the transmitter and the stability and homogeneity of the magnetic field are crucial, for the resonance peak separations which are to be measured may correspond to changes in frequency or field in the order of a few parts in 10^9. Ordinary electronic regulation of the electromagnet current is usually not sufficient, so that a special field-stabilizing device, frequently a galvanometer feedback amplifier, is used rapidly to correct any tendency toward fluctuation of the field strength; this must be connected so that it still permits the desired linear sweep necessary to scan the spectrum. Very large magnet pole faces are used, and the specimen cross section is kept as small as possible to increase field homogeneity over its area. Inhomogeneity transverse to the specimen tube axis is further nullified by spinning the tube, usually mounted on the rotor of a small air turbine, at several hundred revolutions per minute. This succeeds because of the direct intervention of the Heisenberg uncertainty principle, which states that it will not be possible to measure a sufficiently small change, ΔE, in the energy of the system in a sufficiently short interval of time, Δt, such that

$$\Delta E \cdot \Delta t \leqslant \hbar$$

Provided the transverse inhomogeneities are sufficiently small to begin with, the spread of energy levels associated with these inhomogeneities is narrowed, in effect, to a single average value.

Line width in the NMR spectra of liquids may be influenced by two factors, aside from residual inhomogeneity of the applied field (which is common). The lifetime of a quantum stationary state is of the order of $2T_1$; consequently the associated energy is spread, i.e., rendered uncertain, over a range of order $\hbar/2T_1$, and this spreads the resonance frequency over a range of the order of $1/4\pi T_1$. For liquids having a very short T_1 this uncertainty broadening can become significant. Another kind of broadening, known as direct dipolar broadening, is due to the varying local magnetic field produced at a nucleus by the neighboring nuclear magnets. That component, in the direction of the applied field, of the local field due to neighboring

magnetic dipoles very nearly averages to zero in liquids where the molecules are tumbling freely; but in viscous liquids, where tumbling is inhibited, the effect can become sufficiently important to obliterate the spectrum.

Instead of the direct measurement of absorption of power from the rf transmitter, most instruments adapted to the determination of the high resolution spectra of liquids, including the commercially available unit manufactured by Varian Associates, Palo Alto, Calif., use the double coil nuclear induction method originally devised by Bloch, Hansen, and Packard (41). The rf field is applied by a transmitter coil with its axis perpendicular to the direction of the steady magnetic field, while the resonance condition is detected with a receiver coil mounted so that its axis is perpendicular to that of the transmitter coil and as well to the magnetic field. The specimen, contained within a cylindrical glass cell, is placed inside the receiver coil. The output of the receiver coil is fed into a high gain rf amplifier, then rectified; the resulting d.c. voltage is displayed on an oscilloscope or recording voltmeter.

With a perfectly orthogonal arrangement of receiver and transmitter coils there is no direct inductive coupling between them; the induced e.m.f. in the receiver coil arises solely from the magnetic flux generated by the nuclear spins. This alternating flux is found to consist of a component in phase with the applied rf magnetic field and a second component in quadrature, i.e., 90 degrees out of phase, with the field. The amplitude of the in-phase component is proportional to the absorption. The amplitude of the quadrature component is proportional to the dispersion. One is usually interested in the pure absorption signal; the dispersion signal resembles a derivative function of the absorption, and its admixture with the absorption signal results in a resonance line whose appearance is highly distorted. Consequently, when an ordinary receiver is used, perfect balance of the probe is purposely avoided, and it is customary to provide for the introduction of a considerable in-phase leakage between transmitter and receiver coils. Adjustment of the amount of leakage is accomplished with a small metallic paddle located off the axis of the transmitter coil. When a substantial leakage signal is introduced, the effect of the quadrature component upon the resultant signal approaches phase modulation rather than amplitude modulation, so that the dispersion mode does not appear in the output of the

AM detector. However, instabilities in the base line of the spectrum due to microphonic changes in the leakage coupling or to transmitter power fluctuations are proportional to the amount of leakage, so the latter will have some optimum intermediate value. The necessity for this compromise is avoided with the newer Varian Associates equipment for use at 60 Mc./sec.; an rf-phase sensitive detector is employed to discriminate between absorption and dispersion components, so that the probe may be operated at perfect balance with zero leakage. The base line stability characteristic is much improved. Operation at 60 Mc./sec. itself offers an advantage in the improvement of the sensitivity factor; moreover, since the chemical shift is proportional to the applied field or frequency while the spin-spin coupling (see Section IV) is independent of these, a higher operating frequency results in less overlap of spin-spin multiplets and a more easily interpretable spectrum.

Williams (42) has given a critical evaluation of such aspects as saturation, magnet stability, field homogeneity, leakage voltage, tuned circuit loading, and detector distortion as they affect quantitative determinations.

III. The Chemical Shift

A. SHIELDING CONSTANTS

The first observation that the resonance frequency for a given nucleus in a given field depends on the chemical form in which the element appears was made by Knight (1) in 1949. Indeed, the fact that the magnetic field actually present at the nucleus differs significantly from the field applied to the specimen is fundamentally responsible for any and all applications of nuclear magnetic resonance to chemistry. The magnitude of applied field (H^0) is altered by the matter through which it must pass in its path to the nucleus and by the operation of several shielding mechanisms differing in detail and in their intra- or extramolecular character.

The total shielding effect is directly proportional to the magnitude of the applied field, as expressed in the equation

$$H_i = H^0 (1 - \sigma_i)$$

where H_i is the field at nucleus i; H^0 is the field applied to the specimen; and σ_i is the nondimensional shielding or screening constant of

nucleus i. The shielding is produced by the entire electronic system surrounding the nucleus. Ramsey (2) has accounted for the effect theoretically and calculated its magnitude in the case of molecular hydrogen; unfortunately, the calculation cannot be made for many molecules because it requires a knowledge of excited-state molecular wave functions which generally are not known. Ramsey's calculation indicated a value of $\sigma = 26.6 \times 10^{-6}$ for molecular hydrogen compared to the bare proton; σ for other protons can be obtained by measurement of the position of resonance relative to molecular hydrogen or to some reference substance having been related to the latter. Thus the σ for the protons of water is 26.0×10^{-6}.

B. STANDARDIZATION

Since shielding constants will probably be obtained precisely only by measurement for some time, they are more commonly expressed in terms of a chemical shift of resonance position from that of a reference substance. The shift may be given in gauss or in cycles per second, at some specified field or frequency; since the magnitude of the shift is proportional to the applied field, a number, δ, obtained by division of the actual separation in gauss by the applied field, is useful for comparison of results obtained under different operating conditions

$$\delta = (H_c^0 - H_r^0)/H_r^0$$

where, at a given transmitter frequency, H_c^0 is the field required to produce resonance in the sample substance, and H_r^0 is the resonant field of the reference compound (3). The sign convention adopted here is such that δ increases with shielding in the sample substance, the definition of Gutowsky *et al.* (3) having been reversed; δ is usually expressed in parts per million (p.p.m.). The shift, δ, may also be obtained by division of the separation δ_ν, given in cycles per second on a frequency scale, by the applied frequency ν^0.

$$\delta = \delta_\nu/\nu^0$$

In practice a spectrum is usually calibrated on a frequency scale with the use of the sideband technique (4). With a fixed transmitter frequency, the spectrum is scanned by a slowly increasing or decreasing sweep of the magnetic field; the field is simultaneously modulated by an audio voltage of known frequency applied to the

sweep coil. This audio modulation of the received signal results in the addition to the spectrum of two satellite peaks identically spaced on either side of each of the original peaks. The scale of any NMR spectrum can be expressed in frequency units at constant field, even though it was obtained with a fixed frequency and variable field, and on a frequency scale the separation of either of the satellite peaks from the original peak is equal to the audio modulation frequency used. Any desired number of points on the scale can thus be calibrated by the use of various audio frequencies.

A suitable reference compound will give one or more sharp, well-separated lines; for organic work, water, benzene, toluene, chloroform, *tert*-butyl alcohol, *tert*-butylamine, and tetramethylsilane, among others, have found favor. An early method of standardization consisted in the substitution of the reference for the sample before and/or after the sample spectrum was run, but this procedure introduces a greater possibility of error due to drift in the field over the time required for the operation. A split rf coil has been used (3) to accommodate both sample and reference. An "internal reference" is some substance which is added in the amount of one or two drops directly to the solution containing the sample. An "external reference" is not mixed with the sample but sealed in a small capillary tube placed inside the sample tube containing the liquid or solution to be examined; the spectrum may be observed without superimposed reference peaks if the capillary is shaken to the top of the tube before the tube is introduced into the probe. For precise work, special sample containers are used which hold the reference liquid in a concentric annular volume surrounding the sample (20,49).

The magnetic field reaching a given nucleus will depend on the electronic system within the molecule, but it will also be altered by the surrounding medium. A molecule of a specimen to which is applied the field H^0 will actually find itself in a field

$$H^0(1 - \alpha\kappa)$$

where κ is the volume diamagnetic susceptibility of the medium, and α is a constant which depends on the shape of the sample (5a,23). Values for α were found to range from 2.3 to 3.0 for a variety of binary mixtures in cylindrical sample tubes oriented transversely to the field (6). The volume (or bulk) diamagnetic susceptibility effect is such that resonance of a given nucleus will occur at a lower applied

field the larger the (negative) κ of the substance or solution. Thus the methane resonance appears 1.95 p.p.m. lower at infinite dilution in carbon tetrachloride than in the gaseous state; even larger solvent shifts were found for fluorine resonances (58). Molecular and bulk effects were separated by Bothner-By and Glick (6) who showed that the equation

$$H = H_i^0(1 - \sigma_i')(1 - \alpha\kappa)$$

holds for "regular" or "well-behaved" solutions where neither sample nor reference contains magnetically anisotropic groups and where chemical association or reaction between the components does not occur. Here H is the resonant field for a bare proton at the frequency employed; H_i^0 is the field which must be applied to the specimen to cause resonance of nucleus i; and σ_i' is the intramolecular shielding factor for nucleus i, imagined to depend only on molecular structural parameters. Deduction of σ_i' or direct comparison of H_i^0 observed with liquids of different volume susceptibility is generally not possible unless the correction is applied; moreover, since a solute will generally have an (unknown) volume susceptibility different from that of its solvent, H_i^0 will show concentration dependence.

Assuming that all components form a regular solution, the chemical shift from an *internal* reference line will be independent of both solvent and concentration. Since the internal reference substance is mixed with the solution, the reference lines are subject to the same volume susceptibility correction as those arising from the sample; ideally, the reference lines shift along with the sample lines on dilution, maintaining a constant separation. This is expressed in the equation

$$H_c^0(1 - \sigma_c')(1 - \alpha\kappa) = H_r^0(1 - \sigma_r')(1 - \alpha\kappa)$$

so that

$$\delta = (H_c^0 - H_r^0)/H_r^0 = (\sigma_c' - \sigma_r')/(1 - \sigma_c') \cong \sigma_c' - \sigma_r'$$

Instances of irregular behavior arise (7) whenever there is a possibility of a preferred orientation of magnetically anisotropic molecules adjacent to the molecule under study. The orientational effect may be largely eliminated by surrounding the molecule with solvent molecules which are more nearly magnetically isotropic; for this reason the relatively spherical carbon tetrachloride is most commonly used as a solvent, whereas the internal reference of choice is tetramethyl-

silane (48), which similarly has a low anisotropy. Tetramethylsilane is additionally convenient because it contributes a single sharp line near the extreme high end of the range of observed organic proton chemical shifts, where it is unlikely to obscure the resonance peaks due to the sample. If the substance being examined tends to associate in solution and is magnetically anisotropic itself, deviations from regular behavior will still appear but can be eliminated by measurements at various concentrations with extrapolation to infinite dilution.

In the case that a concentric cylindrical *external* reference is used it is found that the resonance position H_r^0 of the reference line is independent of the volume susceptibility of the surrounding sample liquid (7); although the resonance peaks of the sample may shift with solvent and concentration, the external reference peak will not. When an external reference is used, one commonly measures the desired separation from the reference line at different concentrations and obtains the chemical shift at infinite dilution by extrapolation. The number obtained in this way will differ from that obtained with the internal reference technique, above, by an amount equal to the change in H_r^0 as the reference is examined first neat and then at infinite dilution in the same solvent, an amount that can be estimated, assuming regular behavior in the reference and solvent, from the difference in volume susceptibilities of reference and solvent using the equation given.

C. CHEMICAL SHIFT AND ELECTRONEGATIVITY

Although application of the complete shielding equation of Ramsey (2) to organic molecules has met with insuperable difficulties, its form has suggested easier approaches to specific cases and simpler, albeit less rigorous, treatments. Qualitatively, it seems clear that the applied magnetic field interacts with the motions of the electrons in the system, which thereby contribute a component to the net magnetic field at the nucleus. This electronic component is proportional to the applied field and is usually in the opposite direction. The effect may be considered an internal diamagnetism or magnetic shielding of the nucleus (15). Saika and Slichter (8) divide the contributing factors into three terms: (*1*) the diamagnetic correction for the atom in question, arising largely from the bonding electron during the period it occupies an atomic s-orbital centered about the nucleus; (*2*) a paramagnetic term; and (*3*) the contributions from other atoms.

The magnitude of the shielding should be directly related to the electron density at the nucleus. The more tightly electrons are held by another atom chemically bonded to the nucleus the less effective they are in shielding the nucleus, so that shielding should be affected by the degree of ionic character of the bond and by inductive and resonance donation or withdrawal of electrons by neighboring groups.

The basic thesis that electron withdrawing residues tend to cause chemical shifts to lower fields was demonstrated for F^{19} resonance by Gutowsky, McCall, McGarvey, and Meyer (15) who obtained definite correlations between resonance position and Hammett's σ constant in a large number of *m*- and *p*-substituted fluorobenzenes. Taft (16) more recently showed that Gutowsky's shielding parameters for *m*-substituted fluorobenzenes could be precisely correlated with σ_I, a purely inductive Hammett-type constant, and that shifts in the *p*-substituted fluorobenzenes could be similarly precisely correlated with a suitable weighted average of σ_I and σ_R, with σ_R the corresponding resonance parameter. A similar trend was noted for proton resonance in an early study of ethyl derivatives (9) and in the extensive collection of simple organic groups of Meyer, Saika, and Gutowsky (3). For example (ref. 3), the average value of δ ($\times 10^{-6}$, relative to external water reference) for the hydroxyl protons in a series of alcohols was -0.10, in a series of phenols, -2.30; in carboxylic acids, -6.40; and in sulfonic acids, -6.60. Similar results were observed for protons bonded to carbon; saturated *C*-methyl groups appeared near $+4.10$, *N*-methyls near $+2.50$, and *O*-methyls at $+1.60$. According to the data of ref. 3 there is remarkably little difference between the resonances of methyl protons attached to the various halogens (CH_3F, $+2.30$; CH_3Cl, $+2.30$; CH_3Br, $+2.10$; CH_3I, $+1.80$) in spite of the wide variation in electronegativity of the halogens. Dailey and Shoolery (10) pointed out that this anomaly and others might arise from the fact that the measurements were made with the pure liquids, with significantly different volume susceptibilities (see Section III-B) so that the δ values would not reflect purely intramolecular phenomena. They proposed the use of the methyl groups in ethyl derivatives as internal references for the methylene shifts. Assuming that the electron-withdrawing power of the substituent group is nearly completely attenuated by the C—C bond, ($\delta_{CH_3} - \delta_{CH_2}$) should be a better measure of the intramolecular effect. In the case of the ethyl halides, an excellent linear

relation with the Huggins electronegativity (11) of the halogen was obtained

$$\text{Electronegativity} = 0.02315\ (\delta_{CH_3} - \delta_{CH_2}) + 1.71$$

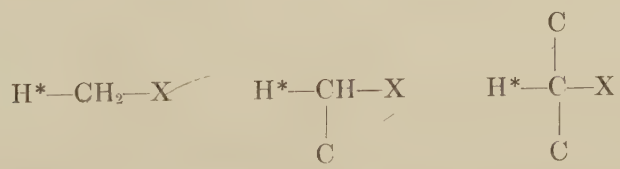
Similarly, Allred and Rochow (12) found a very large effect on the relative chemical shifts of the methyl halides as the concentration in carbon tetrachloride solution was decreased, attributed almost entirely to corresponding changes in the volume susceptibility; the chemical shift value extrapolated to infinite dilution was found to be a linear function of the Huggins electronegativity of the halogen. The assumption that the electron withdrawing effect of the halogen is attenuated in the C—C bond of ethyl derivatives was shown to be approximately correct, but at infinite dilution in carbon tetrachloride the methyl resonance of ethyl chloride actually appeared at a slightly *higher* field than with ethyl bromide.

Bothner-By and Glick (7) determined the resonance position (H_p^0) for the *para* hydrogen in ten mono-substituted benzenes in the pure liquid and as extrapolated for the infinitely dilute solution in carbon tetrachloride. Although the peaks for the pure liquids do not seem to fall in any recognizable order, those found by extrapolation follow the order expected from the electrical effects of the substituents, and, within experimental error, fit the equation

$$H_p^0 - H_0^0 = -5.0\sigma_p$$

where H_0^0 is the extrapolated resonance field for benzene, and σ_p is Hammett's *para* substituent constant.

Although many essential regularities thus support the effect of electron density on shielding, there remain a number of anomalies, phenomena which cannot be deposed even by volume susceptibility correction. Progressive substitution of hydrogen by carbon in a simple series such as



leads in each instance to decreased shielding of the asterisked proton so substantial as to belie explanation in terms of the small electro-

negativity difference ($X_C - X_H$) = 0.4 (11); proton resonance in *C*-methyl groups occurs about 0.37 p.p.m. higher than in open chain methylenes (14). Protons bonded to olefinic groupings appear at far lower fields than those attached to saturated residues, but protons attached to acetylenic groups appear at *intermediate* positions (3). Aromatic protons are much less shielded than olefinic protons even though the carbon hybridization and electronegativity of attached groups are kept similar. Hydrogen bonding at a hydroxyl proton reduces its resonance position (4,17,21,22,31) so that bridge hydrogens in stable chelates (e.g., acetylacetone enol) (18,80,81,82) appear to be among the least shielded known, although a naive view might predict the electron density at a hydrogen-bonded proton to be higher than that of the corresponding dissociated or nonbonded hydroxyl. A proton attached directly to a carbonyl group, as in an aldehyde, also appears at very low fields, but the organic chemist is not accustomed to regard the aldehyde C—H bond as very ionic. Highly acidic protons are as unshielded, but the aldehyde hydrogen is not acidic.

It would be a subtle argument based on ionic character or electronegativity that might be invoked in explanation of the stereochemical configurational effects upon chemical shift in the spectra of acetylated carbohydrates recently reported by Lemieux, Kullnig, Bernstein, and Schneider (19). In these derivatives there is a shift of 0.12–0.25 p.p.m. between the signals for the methyl hydrogens of equatorial and axial acetoxy groups and a shift of approximately 0.20 p.p.m. between the signals for axial and equatorial hydrogens. The carbon-1 hydrogens of anomeric acetylated aldopyranoses produce signals which are separated by 0.25–0.65 p.p.m. when these hydrogens are axial in one of the anomeric forms and equatorial in the other. Similar stereochemical effects have been noted in hydroxylated steroids by Shoolery and Rogers (20); the axial ring hydrogen atoms are shifted to fields 0.5–0.6 p.p.m. higher than the equatorial

Bothner-By (13) has provided an interesting illustration of the general operation of some additional factor in Figure 1, which compares the shieldings of the methyl derivatives of the first row elements (carbon, nitrogen, oxygen, fluorine) with those of the methyl halides as a function of electronegativity. Plotted are the resonance positions of *n*-hexane, trimethylamine, dimethyl ether, methyl fluoride (12), methyl chloride (14), methyl bromide (14), and methyl

iodide (14); it is seen that the points fall close to two straight lines of different slope, and the protons in the higher methyl halides are clearly progressively less shielded than would be expected from the electronegativities alone.

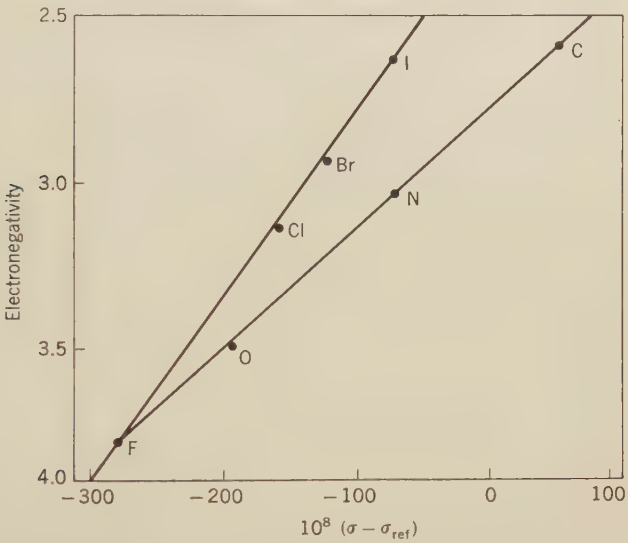


Fig. 1. Shieldings in methyl derivatives as a function of electronegativity. (From A. A. Bothner-By and C. Naar-Colin, ref. 13; reproduced with permission of the authors and publisher.)

D. CHEMICAL SHIFT AND MAGNETIC ANISOTROPY

According to current belief, the instances of behavior inimical to the simple correspondence of proton shielding with electron density can be associated with the presence of neighboring magnetically anisotropic groups (see McConnell, ref. 28). A magnetically anisotropic group is one whose molecular magnetic susceptibilities along three perpendicular axes are not all identical; in principle any electronic system will be anisotropic unless it possesses spherical or equivalent symmetry. The magnetic effect on a nucleus by neighboring magnetically isotropic groups averages to zero in a liquid over a short time because thermal motion induces a rapid random change in the direction of H^0 with respect to the molecular axes. The molecular susceptibility of benzene is much larger along the cylindrical six-fold

axis than along axes in the plane (25); it was proposed by Pople (24) that the anisotropy would allow explanation of the relative chemical shifts of ethylenic and aromatic protons. The principal magnetic difference between the open-chain double bond and the aromatic system lies in the fact that in the aromatic ring an electronic current can flow around a closed conjugated path of relatively large radius. The π-molecular orbital system is visualized as a circular superconductor through and around which the mobile electrons will precess while under the influence of the applied field H^0 (more exactly that component of H^0 which is perpendicular to the plane of the ring). The supercurrent generates magnetic flux lines with roughly the shape of a toroidal shell (Fig. 2), whose contour Pople

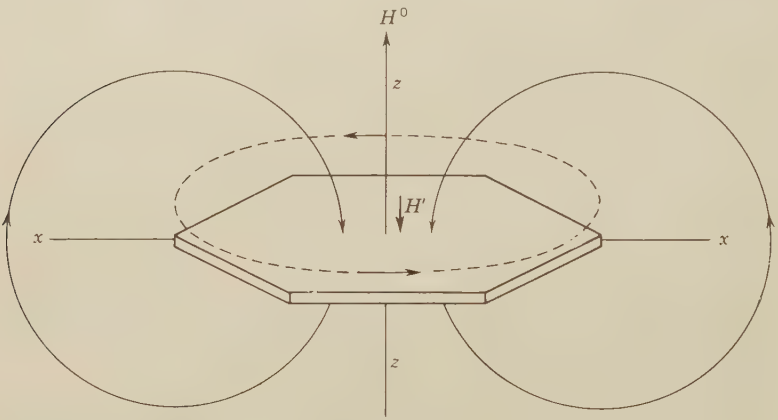


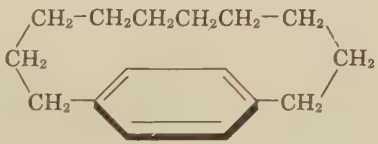
Fig. 2. Magnetic anisotropy in the aromatic ring. Only two of the induced magnetic flux lines are shown.

approximated by the field of a magnetic dipole H' located at the center of the hexagon with its axis parallel to and opposed to H^0. In a region (x) near the aromatic protons, the induced lines of force actually add to H^0 and the result of this reinforcement is that a lower applied field is necessary to induce resonance. Calculation of the magnitude of the effect by classical electromagnetic theory showed that it should be of the correct order to explain the difference observed.

Thus, with six electrons in circulation, the induced diamagnetic dipole (24) has the magnitude $3e^2Ha^2/2mc^2$, where e is the electronic charge, H is the applied field, a is the radius of the circular

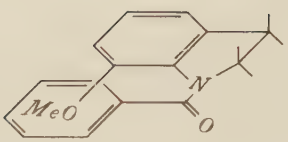
superconductor (taken as the C—C distance), m is the electronic mass, and c is the velocity of light. This model is known to give a satisfactory estimate of the diamagnetic susceptibility of benzene (25). The secondary field due to the magnetic dipole at the proton position is $3e^2Ha^2/2mc^2\ (a + b)^3$, where b is the C—H bond length. Since the real molecule is not in a fixed orientation with respect to the applied field but tumbling randomly in solution, the effect must be averaged over all directions (multiplied by the factor $^1/_3$ in this case). The resulting expression for the additional shielding is $-e^2a^2/2mc^2\ (a + b)^3$; substitution of the appropriate constants give -1.7×10^{-6}, in good order of magnitude agreement with the observed difference, -1.4×10^{-6}, between benzene and ethylene.

Waugh and Fessenden (26) refined the calculation by eliminating the point dipole approximation and by noting that the π-current is not confined to the plane of the aromatic ring but has its maximum density in two regions on either side; *ad hoc* agreement with the chemical shift from cyclohexadiene to benzene protons is obtained if the two current loops are separated by about 0.9 A., which is about the distance estimated between the two centers of maximum electron density in the carbon $2p_z$ orbital. Very strong support for the essential premise of the Pople theory was uncovered in an examination (26) of the 1,4-polymethylenebenzenes (e.g., I) when it was found that the methylene groups held above the center of the aromatic ring were considerably *more shielded* than normal in saturated cyclic polymethylenes.

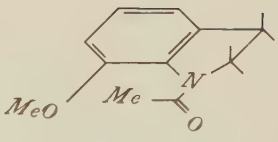


(I)

Although the induced moment reinforces the applied field at points (x) outside the ring radius near the equatorial plane (Fig. 2), it has the opposite effect, cancellation, at points (z) near the sixfold axis. A similar example was found in the natural products field (27) in an NMR study of aspidospermine derivatives; in carbon tetrachloride solution the *O*-methyl resonance of N_a-benzoyldeacetylaspidospermine (part structure II) is shifted 0.73 p.p.m. to higher fields from the corresponding peak of aspidospermine (III) itself; again, in II, the



(II)



(III)

O-methyl is situated directly above the center of the aroyl nucleus, into which it is pressed by the tendency toward coplanarity of the amide linkages. It seems likely that at least part of the large shift in the resonance of aliphatic protons caused by the introduction of a phenyl group is due to the effect of the benzene ring anisotropy; "benzylic" hydrogens appear about 1.5 p.p.m. to lower fields than their similarly substituted saturated aliphatic counterparts.

It was suggested (24) that the upward shift (3) of the acetylenic hydrogen (relative to the olefinic) can be interpreted in terms of a similar diamagnetic precession about the cylindrical axis (Fig. 3).

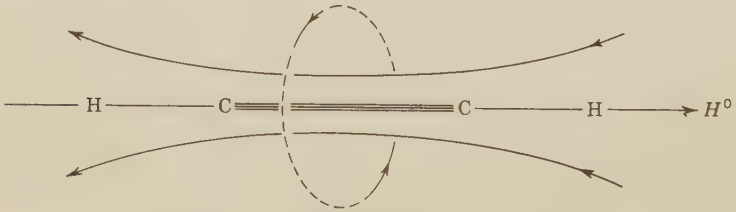


Fig. 3. Magnetic anisotropy in acetylene.

Considering that component of the applied field parallel to this axis, we see that the induced moment will be equivalent to a secondary magnetic field acting (in the region of the axis, where the proton is attached) against the applied field.

Bothner-By and Naar-Colin (14) observed that the shieldings of the α-protons in isopropyl halides show a slight *increase* as the electronegativity of the halogen increases, an effect which is even more marked with the cyclohexyl halides; the order shown by the methyl halides is thus inverted. Consideration of various no-bond resonance forms offers a possible explanation, but more plausible is the effect of a varying anisotropy of the carbon-halogen bond which acts to cancel or even exceed the shift due to change in electron density.

Characteristic longitudinal and transverse susceptibilities (χ_L and

χ_T) may be assigned to single or triple bonds; double bonds should require three different susceptibilities. In the case of an (axially symmetric) single or triple bond with the proton located at a distance r from the bond midpoint and at an angle β off the bond axis, anisotropy results in an average local field at the proton given by (a point dipole approximation)

$$\langle H_l \rangle_{av} = {}^1/_3 H^0 (3 \cos^2 \beta - 1)(\chi_L - \chi_T) r^{-3}$$

after allowance for thermal tumbling (13,14,28). If $\chi_T > \chi_L$, then protons so located that β is greater than 54° 44′ will be more shielded, whereas those for which β is less than this value will be unshielded by the bond. The transverse susceptibility χ_T represents the difference between a diamagnetic term and a second-order paramagnetic term; a method for the estimation of the latter contribution has been given by Pople (30) and applied to the calculation of chemical shifts of hydrogen fluoride, water, ammonia, and methane. For haloalkanes Bothner-By and Naar-Colin (14) suggest that in the series methyl, primary, secondary alkyl and in the series fluorine, chlorine, bromine, iodine the diamagnetic anisotropy of the C—X bond is progressively increased through the diminution of the paramagnetic term as the bond becomes more ionic and the halogen more nearly approaches the (spherically symmetrical) state of the halide ion for which no paramagnetic contribution is possible. With methyl halides (see Fig. 1) the consequences of electronegativity still override the increasing unshielding effect of anisotropy in the series fluorine, chlorine, bromine, iodine, but in the secondary halides electronegativity shifts are cancelled or exceeded.

These principles can be extended to the olefinic double bond. Consideration of the shape of the π-molecular orbital system, which should allow a qualitative decision on the most efficient mode of electron circulation, suggests that the longitudinal susceptibility χ_L now will be the smallest, that χ_T, the transverse susceptibility in the plane of the nuclei, will be the largest, and that $\chi_{T'}$, the susceptibility perpendicular to this plane, will probably be intermediate in magnitude. It is seen that the result of anisotropy in this model (Fig. 4) should be that protons directly attached to the double bond, and as well any "allylic" protons on carbon attached to the double bond, will be in an unshielded region. It certainly is true that allylic proton resonances occur at lower fields, and olefinic proton resonances

at far lower fields, than those of comparable saturated systems, but it is not yet clear how much of the shift is due to a difference in electronegativity of the saturated versus unsaturated substituents. The model (Fig. 4) predicts that the region of *maximum* shielding will be on the transverse axis *in the plane* of the double bond; this prediction does not appear to have been tested experimentally as yet although work is proceeding in this direction in several laboratories.

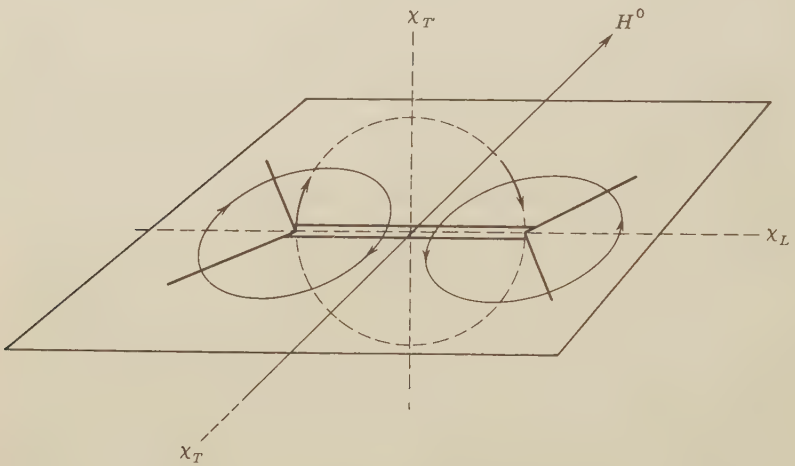


Fig. 4. Magnetic anisotropy in the π-bond. Only two of the induced magnetic flux lines are shown.

A rationalization of the effect of hydrogen bonding (31) in unshielding a hydroxyl proton has been given (14) in terms of the expected large transverse diamagnetism of the electrostatically deformed orbital of the oxygen to which the bond is made. Using the concept of neighboring C—C bond anisotropy and the ensuing dependence of shielding on molecular geometry, the same authors (13) have briefly discussed the quantitative relation of conformation in alkanes and cycloalkanes to chemical shift; they have also suggested that the difference in shielding between methyl and methylene in normal saturated hydrocarbons might be ascribed to the action of anisotropy of two neighboring C—C bonds upon the methylene protons whereas the methyl hydrogens are acted upon by only one.

E. STANDARDIZED VALUES OF CHEMICAL SHIFT

Table I contains values of chemical shift selected for their utility in general CH group analysis. The numbers have been taken from the much more extensive collections of Bothner-By, Naar-Colin, and Shapiro (64) and of G. V. D. Tiers (65); values are based on the "τ" scale (48) adopted by these investigators, which assigns the arbitrary chemical shift of 10.00 (p.p.m.) to tetramethylsilane in carbon tetrachloride solution at infinite dilution. It is hoped that this scale will come into general usage. Many of the values given are the result of extrapolation to infinite dilution in carbon tetrachloride, and those which are not extrapolated are for quite dilute ($\lesssim 10\%$) solutions. A variety of reference substances has been used in the actual measurements, so that the figures designated "a" are linked to tetramethylsilane only by calculation. The probable error in the figures given is ± 0.025 p.p.m., except where otherwise stated.

TABLE I
Table of Standardized Chemical Shifts[a]

Compound	Shift	
Methyl Protons, CH_3X		
$(CH_3)_4Si$	10.000	
$(CH_3)_2S$	7.942 ± 0.002	b
$(CH_3)_3N$	7.876 ± 0.007	b
CH_3I	7.843 ± 0.004	b
$(CH_3)_2NCH_2C_6H_5$	7.83	b
$(CH_3)_2NCH_2CH_2OH$	7.73	a
CH_3Br	7.38	a
CH_3SCN	7.394 ± 0.002	b
$(CH_3)_2NCHO$	7.22 two lines	b
	7.08	
CH_3Cl	7.00	a
$(CH_3)_2NC_6H_5$	7.096 ± 0.005	b
$(CH_3)_2O$	6.73	a
CH_3OH	6.622 ± 0.003	b
$(CH_3)_2SO_3$	6.38	a
$CH_3OC(O)CH_3$	6.33	a
$CH_3OC_6H_5$	6.267 ± 0.002	b
$(CH_3O)_2CO$	6.20	a
$(CH_3)_2SO_4$	6.03	a
CH_3F	5.70	a
CH_3NO_2	5.720 ± 0.002	b
Methyl Protons, CH_3C		
$CH_3CH_2CH_2CH_2CH_3$	9.15	a
$(CH_3)_4C$	9.08	a
Camphene	8.99	b
CH_3CH_2OH	8.83 ± 0.02	b
$CH_3COOCH_2CH_3$	8.79	b
CH_3CH_2Cl	8.60	a
$(CH_3)_2CHCl$	8.46	b
CH_3CH_2Br	8.34 ± 0.01	b
1-Methylcyclohexene	8.40	b
$(CH_3)_2CHBr$	8.29 ± 0.02	b
Pinene (allylic CH_3)	8.37	b
$(CH_3)_2C{=}CH_2$	8.299 ± 0.002	b
	8.28	b

(*continued*)

Table I (*continued*)

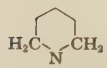
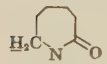
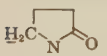
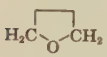
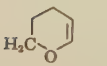
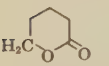
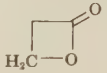
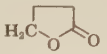
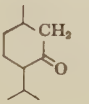
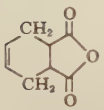
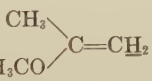
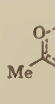
Compound	Shift	
Methyl Protons, CH_3C		
$(CH_3)_2CHI$	8.12 ± 0.02	b
$H_2C{=}C(CH_3)CH{=}CH_2$	8.16	b
CH_3CN	8.026 ± 0.002	b
$C\underline{H}_3COOCH_2CH_3$	8.05 ± 0.02	b
CH_3COOCH_3	7.95	a
CH_3COCH_3	7.915 ± 0.003	b
$CH_3C_6H_5$	7.663 ± 0.003	b
$CH_3COC_6H_5$	7.45 ± 0.02	b
CH_3COBr	7.15	a
Methylene Protons, CCH_2X		
$(CH_3CH_2)_3N$	7.58	b
	7.31	b
$CH_3CH_2NH_2$	7.22	c
	6.88	
$CH_3CH_2CH_2I$	6.80 ± 0.02	b
$(CH_3CH_2)_2O$	6.64 ± 0.02	b
$CH_3CH_2CH_2Br$	6.64 ± 0.02	b
	6.63	b
$CH_3CH_2CH_2Cl$	6.53	b
CH_3CH_2OH	6.41 ± 0.02	b
	6.37	b
	6.10	b
$H_2C{=}C(Me)C\underline{H}_2Cl$	6.04	b
$CH_3C\underline{H}_2OC(O)CH_3$	5.95	a
	5.91 ± 0.02	b
$HC{\equiv}CC\underline{H}_2Cl$	5.91	b
$HC{\equiv}CC\underline{H}_2OH$	5.82	b
	5.78	b
	5.73 ± 0.02	b
$C_6H_5CH_2OH$	5.61 ± 0.02	b
Methylene Protons, CCH_2C		
Cyclopropane	9.778 ± 0.003	b
$CH_3CH_2CH_2CH_2CH_2CH_3$	8.75 ± 0.02	b
Cyclohexane	8.564 ± 0.001	b
Cyclopentane	8.492 ± 0.001	b
Cycloheptane	8.470 ± 0.005	b
Adamantane	8.218 ± 0.001	b
	8.05	b
	8.04	b
	7.98 single line	b
$CH_2{=}CHC\underline{H}_2C\underline{H}_2CH{=}CH_2$	7.88	b
	7.85	c
	7.84	b
	7.77	b
	7.75	c

Table I (*continued*)

Compound	Shift		Compound	Shift	
Methylene Protons, CCH_2C					
	7.69	b		5.70	a
			$(CH_3)_2CHNO_2$	5.56	b
	7.69	b			
	7.50	a	$(CH_3)_2CHCH_2Br$		
				8.20	b
	7.64	a			
				7.81	b
$(CH_3CH_2)_2CO$	7.61	b			
	6.52	b		7.22	b
$CH_3COCH_2COOCH_3$					
	6.52	c			
$CH_3COCH_2COCH_3$	6.45	c			
				6.53	b
Methine Protons,			*Olefinic Protons,* C=CH		
	7.05	a		5.46	b
$(CH_3)_2CHNH_2$	7.05	a			
	7.13	b	$(CH_3)_2C=CH_2$	5.399 ± 0.003	b
$(CH_3)_2CHOCH(CH_3)_2$					
	6.44	a		5.40	b
	6.08	a	$(CH_3)_2C=CHCH_3$		
				4.79	b
$(CH_3)_2CHOH$	6.05	a	$HC\equiv CC(Me)=CH_2$		
				4.70	b
	5.95	b		4.70	b
$(CH_3)_2CHCl$	5.88	a	$(C_6H_5)_2C=CH_2$	4.60	b
	5.88	a		4.52	c
$(CH_3)_2CHBr$	5.83	a			
$(CH_3)_2CHI$	5.73	a			

(*continued*)

Table I (*continued*)

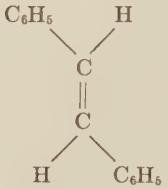
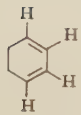
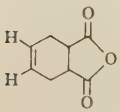
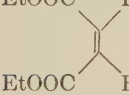
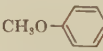
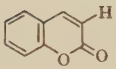
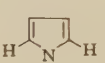
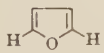
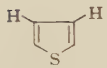
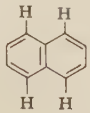
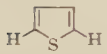
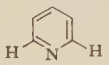
Compound	Shift		Compound	Shift	
Olefinic protons, C=CH			$CH_3CH\underline{=}CH—CHO$		
				3.15	b
	4.43	b			
	4.28	b		2.992 ± 0.004	b
	4.22	b	*Acetylenic Protons*, C≡CH		
			$HOCH_2C\equiv CH$	7.67	b
			$ClCH_2C\equiv CH$	7.60	b
	4.18	a	$CH_2=C(CH_3)-C\equiv CH$	7.29	b
	4.14	a	$C_6H_5C\equiv CH$	7.07	b
			$CH_3COC\equiv CH$	6.83	a
			Aldehydic Protons, CCHO, XCHO		
	4.06	b	$(CH_3)_2N—CHO$	2.16	b
			CH_3OCHO	1.97	b
$CH_3CH=C\underline{H}CHO$	3.95	b	$(CH_3)_2CHCHO$	0.44 ± 0.01	b
EtOOC H			$C_6H_5CH=CHCHO$		
	3.84	b		0.37	b
			CH_3CHO	0.284 ± 0.002	b
	3.76 ± 0.01	b		0.199	b
			C_6H_5CHO	0.035	b
	3.72	b	*Aromatic Protons*		
	3.58	b		3.94 ± 0.01	b
$Cl_2C=CHCl$	3.548 ± 0.003			3.72 ± 0.01	b
$C_6H_5CH=C\underline{H}—CHO$					
	3.36	b		3.47 ± 0.01	b
	3.35	b	Mesitylene	3.356 ± 0.004	b

Table I (*continued*)

Compound	Shift		Compound	Shift	
Aromatic Protons				2.643 ± 0.007	b
	2.94	b	C_6H_5CN	2.464 ± 0.004	b
Toluene	2.905 ± 0.003	b		2.27	b
	2.83	b			
Benzene	2.734 ± 0.003	b		1.50	b

[a] Values designated "a" are taken from ref. 64; values designated "b" are from ref. 65. The author is very grateful to Dr. Bothner-By and to Dr. Tiers for their kind permission to include these values in advance of publication. Values designated "c" are taken from ref. 18. In cases where the molecule contains two or more different groups conforming to the heading, the proton(s) responsible for the chemical shift given is underlined.

IV. Spin-Coupling

A. MECHANISM

As explained in Section III, differently situated magnetic nuclei within a molecule give rise to resonance lines chemically shifted from one another as a result of differences in electronic shielding. Improvement of instrumental resolution over the past few years has been rapid, so that not long after the discovery of the chemical shift it became apparent that the resonance spectra of liquids show fine structure as a result of the mutual interaction of these different nuclei. In Figure 5 (*top*) we see the spectrum of ethanol as it appears with an intermediate instrument resolution; the largest peak is due to the protons of the methyl group, the central peak is due to the methylene group, and the smallest peak at lowest field is due to the hydroxyl proton. Figure 5 (*middle*) shows the spectrum of ethanol, containing a trace of acid, examined with somewhat improved resolution; the methyl peak has been split into a triplet and the methylene peak has become a quadruplet. The spectrum of isopropyl alcohol is given in Figure 5 (*bottom*). The splitting is clearly related to the number of

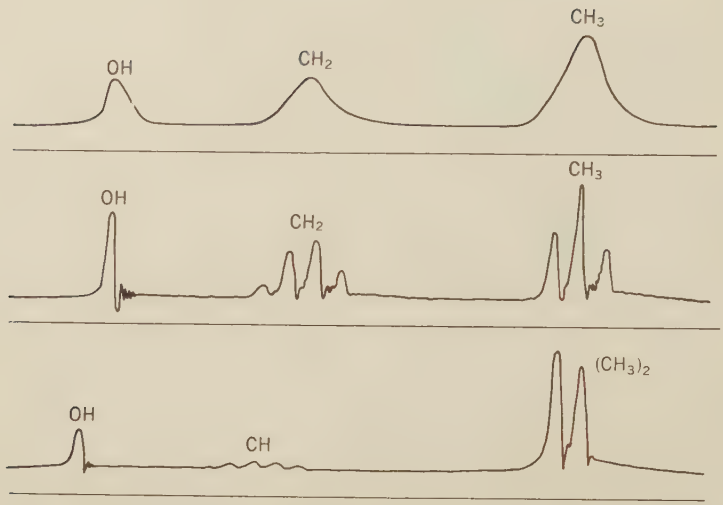


Fig. 5. Ethanol with poor resolution (*top*) and with somewhat better resolution (*middle*); isopropyl alcohol (*bottom*).

protons nearby those generating a given peak. Although fine structure may complicate the spectrum, it is obvious that if such information can be obtained by analysis of the splitting, then the phenomenon should be very useful in structure work.

It is quite clear that the fine structure observed with liquids is not due to the direct magnetic coupling through space of the nuclear spin dipoles, although such coupling is of considerable importance in the treatment of solid state spectra (5b). The component at any nucleus, parallel to the applied field, of the local field produced by direct dipolar coupling can be shown theoretically to average to zero through thermal tumbling (5c). This is confirmed by the empirical fact that resonance in liquids due solely to a number of magnetically equivalent nuclei is never found to be split. Thus, in Figure 5 (*middle*), the fact that the methyl group contains three protons affects the area of the methyl resonance but not its multiplicity. The fine structure is now recognized to be derived from an indirect coupling of the nuclear spins via the bonding electrons. Although the net electronic spin magnetic moment in a covalent bond or closed shell is zero because the electron spins are paired off, a nuclear dipole induces a small magnetic polarization of the bonding electrons (32–34). A nonzero electron spin

density appears at other regions of the bond and, depending upon the degree of electron delocalization, perhaps at distances further removed. A neighboring nuclear dipole interacts with the spin density in that locality and the (quantized) energy of the system depends on the relative orientation of the two nuclear spin moments as well as upon their orientation in the applied field. Such indirect coupling was shown not to average to zero through tumbling in liquids and to provide splittings independent of the applied field of the correct order of magnitude (32); furthermore, as will be seen, the postulated interaction is such that coupling between fully equivalent nuclei will not give rise to observable effects, as required experimentally.

B. APPROXIMATE TREATMENT

A first order approximation, *which works well when the splitting is small compared to the chemical shift*, may help make the situation clearer. Consider proton A and the nonequivalent proton X, within an electron cloud containing no other magnetic nuclei. In the absence of spin-coupling, each proton will give rise to a single resonance line at a characteristic chemically shifted position, so that the spectrum (Fig. 6 (*upper*)) will contain two well-spaced lines at $H_A^0 = H/(1 - \sigma_A)$ and $H_X^0 = H/(1 - \sigma_X)$, where H is the resonant field for the bare proton, and σ_A and σ_X are the shielding constants for A and X. The separation in cycles per second will be $\delta_\nu = (\gamma/2\pi)H(\sigma_A - \sigma_X)$. We now suppose that the protons interact through the electronic system; the field at A will be slightly increased or decreased depending upon which of the two spin orientations, $I_X = \pm 1/2$, is adopted by X. Since the energy difference between the states corresponding to $I_X = \pm 1/2$ is exceedingly small compared to kT at ordinary temperatures, the probabilities of the two X spin orientations are almost exactly equal. The result is that the A resonance line is split into a symmetrical doublet. The same applies to the X resonance line, split into a doublet because of the two possible spin orientations of proton A; the spectrum (Fig. 6B) will then consist of four equally intense lines with the separation between members of the A doublet the same as in the X doublet. The amount of the splitting will be a measure of the ability of the electron cloud to couple the protons; it is designated J, in cycles per second

As examples of the AX system Gutowsky *et al.* (40) offer IV and V. In IV splitting of the proton resonance doublet is 2.0 ± 0.3 c.p.s.

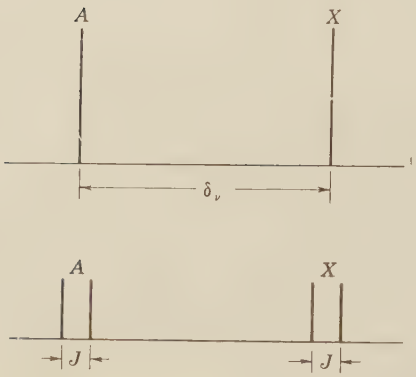
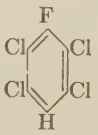
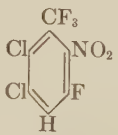


Fig. 6. AX spectra, when protons A and X are uncoupled (*upper*) and when coupled (*lower*).

and of the fluorine doublet, 2.1 ± 0.3 c.p.s. In V the proton lines are split by 8.6 ± 0.8 and the fluorine lines by 8.0 ± 1.7 c.p.s.



(IV)



(V)

The system A_2X, containing two equivalent A protons and one different X proton, can be treated similarly. The A protons are considered equivalent when they have identical shielding constants and when the J-coupling of each to the X proton is identical. The A resonance line is split into a doublet by the two spin orientations $I_X = \pm 1/2$. The X resonance line is split into a symmetrical triplet with the center line twice the intensity of the other two; this is because the total spin M_A of group A_2 can take three possible values (1, 0, −1) with one ($M_A = 0$) twice as probable as the others. The A_2X spectrum for $\delta_\nu >> J_{AX}$ is shown in Figure 7; spectra of this

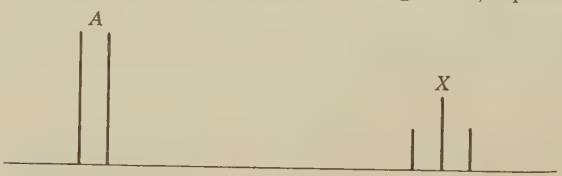
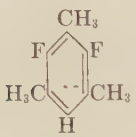
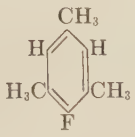


Fig. 7. A_2X spectrum.

type were observed (40) produced by VI, VII, and VIII. The proton spectra of VI and VIII are triplets and that of VII is a doublet,



(VI)



(VII)

(VIII)

with fluorine spectra the reverse. In the same way the system A_3X gives an A doublet and an X quadruplet of intensities 1, 3, 3, 1 corresponding to the four values $M_A = 3/2,\ 1/2,\ -1/2,$ and $-3/2$ resulting from the eight possibilities for three spins in A_3. In general (35,40), when $\delta_\nu >> J_{AX}$ the system A_nX_m containing n equivalent A protons and m equivalent X protons will give an $(m + 1)$-fold multiplet in the A region at frequencies

$$\nu_A = (\gamma/2\pi)H_A{}^0 + J_{AX}M_X$$

and an $(n + 1)$-fold multiplet in the X region at frequencies

$$\nu_X = (\gamma/2\pi)H_X{}^0 + J_{AX}M_A$$

provided again that all A protons are coupled equally to all X protons. Care must be exercised, because structural equivalence of protons A or of protons X does not guarantee that there will be only one J_{AX}. For example, the case of 1,1-difluoroethylene, although properly considered A_2X_2, does not obey the rule because different coupling constants, e.g., $J_{\mathrm{HF}(cis)}$ and $J_{\mathrm{HF}(trans)}$ are required to describe the interactions (38). When the rule does apply, the relative intensities of the components in the A multiplet will be the binomial coefficients of the expansion $(a + b)^m$ and similarly for the X multiplet; for example, when $m = 4$, the five peaks in the A region will have relative intensities 1, 4, 6, 4, 1.

It should be noted that the theory in the qualitative form just given does *not* account for the experimental observation that isolated equivalent protons fail to split their own resonance line; moreover the first approximation breaks down both quantitatively and qualitatively when δ_ν is of the same order as J. The discrepancy is apparent

even in the simplest two-proton system AB where $\delta_\nu \cong J$ and where, instead of four equally intense lines, two stronger and two weaker lines are found. In contrast to the case AX, the separation between the midpoints of the A and B doublets is no longer equal to δ_ν but is larger than that quantity by an amount that depends on J. In the case of A_2B, rather than the simple doublet and triplet of A_2X, the spectrum contains nine lines and these are no longer spaced in any simple manner. The spectra of even moderately larger systems frequently presents a most complex appearance when examined under the high resolution readily attainable today; pyridine, for example, gives rise to at least 110 lines, the majority of which have been observed (36). Since in real systems δ_ν is commonly as small as J, it is fortunate that this phase of the problem has been so successfully treated by quantum mechanical methods; the complete and accurate solution of the Schrödinger equation, as it applies to the interaction of J and σ, can be readily obtained. If σ for each proton and J for each pair of protons is known, the problem of calculation of tens or even hundreds of line positions is a routine performance. If the σ's and J's are not known, spectra can be calculated for a range of parameters until a satisfactory fit is obtained, and here the application of modern electronic computing methods has already been notably successful. It is appropriate, in a discussion of recent advances, for us to devote space to the basic mathematical technique.

C. THE HIGH RESOLUTION HAMILTONIAN

The electron coupled spin-spin interaction is postulated (33,34,38, 50–53) to be of the form

$$E = J_{ij}[\mathbf{I}_i \cdot \mathbf{I}_j]$$

where E is the energy of interaction; J_{ij} is a proportionality constant, the coupling constant describing the magnitude of the interaction; and $\mathbf{I}_i$ and $\mathbf{I}_j$ are the spin angular momentum vectors of nuclei i and j. The equation shows that the energy will depend on the dot product of the two vectors, and hence on the relative spatial orientation of the two nuclear magnets. J will be positive when the state with spins parallel has the high energy. In the presence of an external field H_i at the nucleus i, a field which by convention is directed along the negative z axis, the energy of the system will also depend on the interaction of the nuclear magnet with H_i, as follows,

$$E' = \eta_i H_i I_{i(z)}$$

where $2\pi\eta_i = \gamma_i$, the gyromagnetic ratio of nucleus i, and $I_{i(z)}$ is the z component of the vector $\mathbf{I}_i$. Only the z component is taken because only this component will interact with the steady field H_i along z. The sign convention is such that nuclei with positive spins have high energies. If there are a number of nuclei we introduce a summation; considering both interactions we have

$$\text{Total energy} = \mathcal{H} = \sum_i \eta_i H_i I_{i(z)} + \sum_{i<j} J_{ij} [\mathbf{I}_i \cdot \mathbf{I}_j]$$

which, by postulate, is the correct "high resolution" Hamiltonian for nuclear spin interactions.

We cannot calculate the energy of the system by direct substitution of numbers into the Hamiltonian. The energy will be quantized, that is, there will be various stationary states of the system to which will correspond discrete values of E, $\mathbf{I}_i$, and $\mathbf{I}_j$. In order to find the discrete values of energy and hence the characteristic nuclear magnetic resonance frequencies $\nu = \Delta E/h$, the Schrödinger equation must be used

$$\mathcal{H}\psi = E\psi$$

where E can take the desired discrete values; ψ is a variable of the system (called the wave function), which in this problem merely describes the condition of the various nuclear spins; and $\mathcal{H}$ is the Hamiltonian, which operates on ψ in order to quantize the energy function. As seen above, the Hamiltonian contains within it the information needed to relate a set of spins to energy. We intend to outline the solution for the simplest system, the two proton case AB, for which the Hamiltonian becomes

$$\mathcal{H} = \eta H^0[(1 - \sigma_A)I_{A(z)} + (1 - \sigma_B)I_{B(z)}] + J_{AB}\mathbf{I}_A \cdot \mathbf{I}_B$$

since $H_A = H^0(1 - \sigma_A)$ and $H_B = H^0(1 - \sigma_B)$, where H^0 is the applied field.

1. We describe the spin states by wave functions. A proton, for which the spin I can take two values, is characterized by a function α (if $I = +1/2$) or β (if $I = -1/2$) of an abstract spin coordinate ω. For the two proton system AB there are four spin combinations for which we use the basic functions

$$\left.\begin{aligned}\phi_1 &= \alpha_A\alpha_B\\ \phi_2 &= \alpha_A\beta_B\\ \phi_3 &= \beta_A\alpha_B\\ \phi_4 &= \beta_A\beta_B\end{aligned}\right\} \tag{1}$$

As a condition in the definition of the functions we require that they obey the following relations

$$\int \phi_n^2 d\omega = 1 \qquad \text{(normalization)} \tag{2}$$

$$\int \phi_n \phi_m d\omega = 0,\ n \neq m \qquad \text{(orthogonality)} \tag{3}$$

2. We multiply both sides of the Schrödinger equation by ψ, integrate with respect to ω, and rearrange terms to solve for E

$$E = \int \psi \mathcal{H} \psi d\omega / \int \psi^2 d\omega \tag{4}$$

Each of the four stationary states in which we are interested will be associated with a discrete value of E and with a wave function ψ; the latter is taken as a linear combination of the basic functions

$$\psi = C_1\phi_1 + C_2\phi_2 + C_3\phi_3 + C_4\phi_4 \tag{5}$$

For each state there will be a set of coefficients C_1, C_2, C_3, C_4, such that the corresponding energy E is constant. Using the Variation Method,* E is differentiated with respect to each C; the derivatives are set equal to zero

$$\partial E/\partial C_1 = \partial E/\partial C_2 = \partial E/\partial C_3 = \partial E/\partial C_4 = 0 \tag{6}$$

Straightforward algebraic substitution of eq. 5 into eq. 4, followed by combination with the relations 6, gives a set of linear simultaneous equations known as the secular equation

$$C_1(H_{11} - ES_{11}) + C_2(H_{12} - ES_{12}) + C_3(H_{13} - ES_{13}) + C_4(H_{14} - ES_{14}) = 0$$

$$C_1(H_{12} - ES_{12}) + C_2(H_{22} - ES_{22}) + C_3(H_{23} - ES_{23}) + C_4(H_{24} - ES_{24}) = 0$$

* The reader not acquainted with the Variation Method will find a particularly lucid description in C. A. Coulson, *Valence*, Oxford University Press, London, 1952, pp. 54 ff.

$$C_1(H_{13} - ES_{13}) + C_2(H_{23} - ES_{23}) + C_3(H_{33} - ES_{33}) + C_4(H_{34} - ES_{34}) = 0$$

$$C_1(H_{14} - ES_{14}) + C_2(H_{24} - ES_{24}) + C_3(H_{34} - ES_{34}) + C_4(H_{44} - ES_{44}) = 0$$

where

$$H_{mn} = H_{nm} \equiv \int \phi_n \mathcal{H} \phi_m d\omega$$

and, from eq. 2 and eq. 3

$$S_{mn} = S_{nm} \equiv \int \phi_n \phi_m d\omega = 0 \text{ (if } n \neq m) \\ = 1 \text{ (if } n = m)$$

The four desired energy values are the four roots of the secular equation; the equation has a nontrivial solution only when the determinant of the coefficients C vanishes

$$\begin{vmatrix} H_{11} - E & H_{12} & H_{13} & H_{14} \\ H_{12} & H_{22} - E & H_{23} & H_{24} \\ H_{13} & H_{23} & H_{33} - E & H_{34} \\ H_{14} & H_{24} & H_{34} & H_{44} - E \end{vmatrix} = 0$$

We see that any matrix derived in this way will have the same form, so that a matrix may generally be written down without explicit derivation of its secular equation. In general the n proton problem will involve 2^n spin functions and a matrix with 2^n columns or rows.

3. We next evaluate the matrix elements. It is at this stage that the spin momentum $\mathbf{I}_i$, having taken on the property of an operator, is caused to operate on the wave functions ϕ_m, ϕ_m, ... The basic rules for spin operators are (70)

$$\begin{aligned} I_x\alpha &= {}^1/_2\beta & I_x\beta &= {}^1/_2\alpha \\ I_y\alpha &= {}^1/_2 i\beta & I_y\beta &= -{}^1/_2 i\alpha \\ I_z\alpha &= {}^1/_2\alpha & I_z\beta &= -{}^1/_2\beta \end{aligned} \qquad (i = (-1)^{1/2})$$

where the subscripts indicate the components of the vector operator $\mathbf{I}$ along the coordinates x, y, and z. The quantities $\mathcal{H}\phi_m$, $\mathcal{H}\phi_n$, ..., and hence H_{mm}, H_{nm}, . . ., can always be evaluated by the successive application of these rules. For example

$$\begin{aligned}(\mathbf{I}_A\cdot\mathbf{I}_B)\alpha\beta &= (I_AI_B)_{(x)}\alpha\beta + (I_AI_B)_{(y)}\alpha\beta + (I_AI_B)_{(z)}\alpha\beta \\ &= {}^1/_2[(I_B)_{(x)}\beta\beta + (I_B)_{(y)}i\beta\beta + (I_B)_{(z)}\alpha\beta] \\ &= {}^1/_4[\beta\alpha + \beta\alpha - \alpha\beta] \\ &= {}^1/_2\beta\alpha - {}^1/_4\alpha\beta\end{aligned}$$

This process becomes laborious especially with larger systems, and it is easier to make use of two formulas derived by McConnell *et al.* (38) from the rules for the use of the Hamiltonian with simple product wave functions $\phi = \alpha\beta\alpha\ldots$

$$\text{(diagonal elements)} \qquad H_{mm} = {}^1/_2 \sum_i \eta_i H_i S_i + {}^1/_4 \sum_{i<j} J_{ij} T_{ij}$$

where $S_i = +1$ if i has α spin in ϕ_m, or $S_i = -1$ if i has β spin in ϕ_m, $T_{ij} = +1$ if spins i and j are parallel in ϕ_m, or $T_{ij} = -1$ if spins i and j are antiparallel in ϕ_m.

$$\text{(nondiagonal elements)} \qquad H_{mn} = {}^1/_2 U J_{ij},\ m \neq n$$

where $U = +1$ if ϕ_m differs from ϕ_n only by an interchange of spins i and j, or $U = 0$ otherwise. The determinant for the system AB then becomes

$$\begin{vmatrix} H_{11} - E & 0 & 0 & 0 \\ 0 & H_{22} - E & H_{23} & 0 \\ 0 & H_{23} & H_{33} - E & 0 \\ 0 & 0 & 0 & H_{44} - E \end{vmatrix} = 0$$

where the nonvanishing elements are: $H_{11} = \eta H^0(1 - {}^1/_2\,\sigma_A - {}^1/_2\,\sigma_B) + {}^1/_4 J$; $H_{22} = \eta H^0(-{}^1/_2\sigma_A + {}^1/_2\sigma_B) - {}^1/_4 J$; $H_{33} = \eta H^0({}^1/_2\sigma_A - {}^1/_2\sigma_B) - {}^1/_4 J$; $H_{44} = \eta H^0(-1 + {}^1/_2\sigma_A + {}^1/_2\sigma_B) + {}^1/_4 J$; and $H_{23} = {}^1/_2 J$.

4. The matrix is very easily diagonalized in this case. E_1 and E_4 are obtained immediately; E_2 and E_3 are obtained as the two roots of the quadratic equation represented by the central two-by-two determinant. The energy levels and the four allowed transitions are given in Figure 8. The stationary state wave functions can be obtained by substitution in the secular equation. The relative intensities of the four lines are proportional to the squares of the matrix elements of I_x (if the applied rf magnetic field is along the x-axis) between the appropriate stationary state wave functions.

D. THE TWO-PROTON SYSTEM *AB*

Figure 8 shows the calculated energy levels (34). The four allowed transitions correspond to a change in total spin $\Delta M = \pm 1$. The calculated spectrum, together with predicted intensities, is given in Figure 9. The positions of the lines are given relative to the mean, $^1/_2\eta H^0(2 - \sigma_A - \sigma_B)$. The separation within either the right-hand or the left-hand pair of lines is J. The separation between doublet centers is *not* $\delta_\nu = \eta H^0(\sigma_A - \sigma_B)$ but $(J^2 + \delta_\nu^2)^{1/2} = 2C$. The ratio of the *intensity* of either outer line to that of either inner line is the same as the ratio of the *separation* of inner lines to that of outer lines, i.e., $(2C - J)/(2C + J)$. The general appearance of the spectrum, aside from a scale factor, depends only on the ratio δ_ν/J. When δ_ν/J becomes very large, $(2C - J)/(2C + J) \cong 1$, and the spectrum becomes that of AX (Fig. 6 (*lower*)) with two widely spaced symmetrical doublets. When $\delta_\nu/J \cong 1$, the spectrum is a symmetrical quadruplet with the two outer lines weaker than the two inner lines. When $\delta_\nu/J = 0$ and $(2C - J)/(2C + J) = 0$, the two inner lines merge into a single line at the (identical) resonance field for both protons, whereas the two outer lines fall to zero intensity. The reason for this behavior is that the two outer lines correspond to transitions involving state 3 (Fig. 8), which becomes a pure *singlet* state when $\delta_\nu/J = 0$, while the three other stationary states become pure *triplet;* transitions between pure singlet and triplet states are

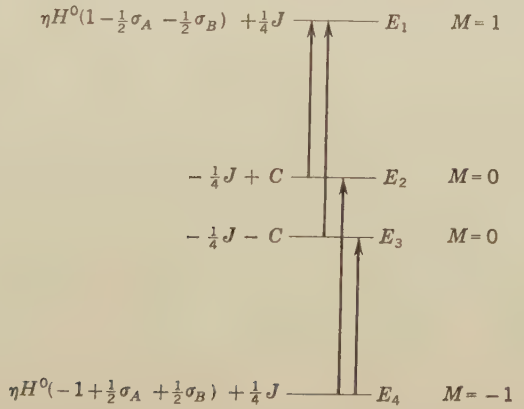


Fig. 8. Energy level diagram for two proton system AB. The variable $C = {}^1/_2\{J^2 + [\eta H^0(\sigma_A - \sigma_B)]^2\}^{1/2} = {}^1/_2(J^2 + \delta_\nu^2)^{1/2}$.

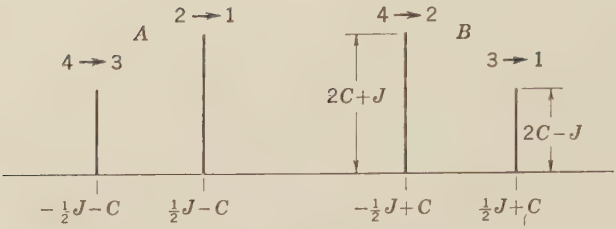


Fig. 9. AB spectrum.

forbidden. The failure of isolated, coupled but magnetically equivalent protons to produce observable splitting in their own resonance is thus a direct result of the quantum mechanical calculation.

Many examples of AB spectra conforming to the predicted pattern have been given (34,35,37,40).

E. THE THREE-PROTON SYSTEM AB_2

The eight energy levels for AB_2 have been calculated by Hahn and Maxwell (34) and by Bernstein, Pople, and Schneider (37). There are nine allowed transitions, the relative intensities of which have also been calculated (37). The appearance of the spectrum, apart from a scale factor, again depends only on the ratio $\delta_\nu/J_{AB} \equiv \delta_\nu/J_{AB'}$; the spectrum is quite independent of $J_{BB'}$. Figure 10 shows the spectrum (when the resonance field of A is lower than that of B) for various values of this ratio.

When δ_ν/J_{AB} is very large, the spectrum is that of AX_2 (Section IV-B). The A lines 2 and 3 coalesce, so that the A resonance becomes a symmetrical triplet with intensities 1:2:1 and with spacing J_{AB}. The four B lines 5, 6, 7, 8 similarly coalesce in pairs to a doublet of spacing J_{AB}. Line 9 is a combination line arising from the simultaneous change of spin orientation of both A and B nuclei. It is forbidden in the limit when δ_ν/J_{AB} is large and is also forbidden in the other limit when $\delta_\nu/J_{AB} \to 0$, so that its intensity is always relatively low.

In the general case when δ_ν/J_{AB} is of the order of 1, there is no pair of lines separated simply by J_{AB} or by δ_ν. For the qualitative identification of the nine AB_2 lines in a spectrum, one may use the following rules derived from the calculated transition energies:

1. The chemical shift position of proton A is given directly by the position of line 3.

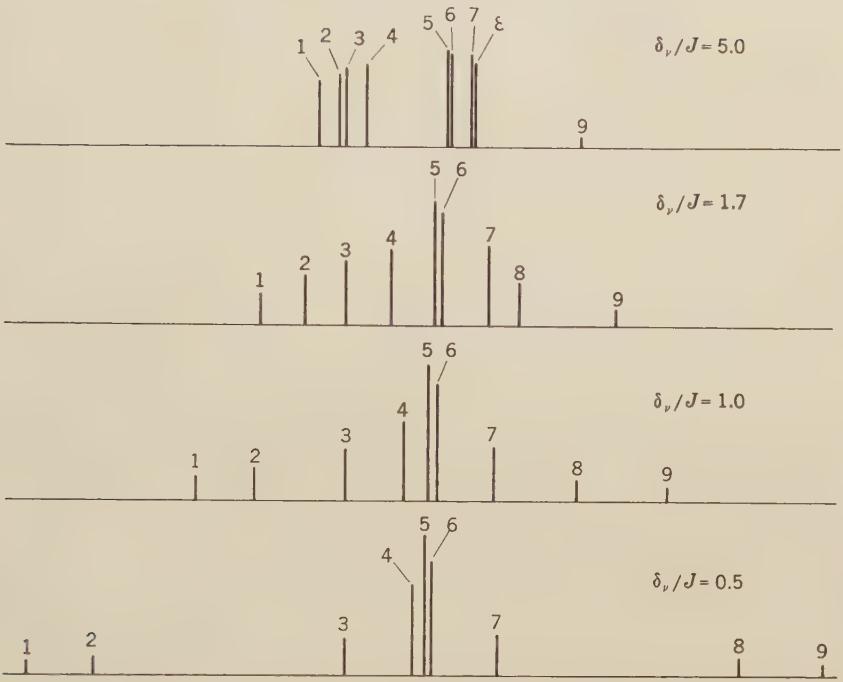


Fig. 10. AB_2 spectrum.

2. The chemical shift position of protons B is given by the arithmetic mean of lines 5 and 7, which must be identical with the arithmetic mean of lines 2 and 9.

3. J_{AB} can be obtained from the relationship

$$J_{AB} = {}^1/_3[\nu_4 + \nu_8 - \nu_1 - \nu_6] \qquad J_{AB} \gtrless 0$$

4. Certain other relationships will hold,

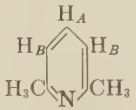
$$\nu_1 - \nu_2 = \nu_3 - \nu_4 = \nu_6 - \nu_7$$

$$\nu_2 - \nu_5 = \nu_4 - \nu_8 = \nu_7 - \nu_9 \qquad J_{AB} \gtrless 0$$

$$\nu_1 - \nu_4 = \nu_5 + \nu_6 - \nu_7 - \nu_8$$

In practice the spectrum is calculated for selected values of the ratio δ_ν/J_{AB} until the best over-all fit is obtained. The ring protons of 2,6-lutidine (IX) gave a spectrum which agrees, in

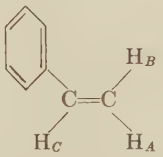
respect to line positions and intensities, with the calculated one within experimental error (37).



(IX)

F. THE THREE-PROTON SYSTEMS *ABC* AND *ABX*

The complete matrix for the general problem *ABC* has been evaluated (37), but its diagonalization is somewhat more difficult owing to the presence of two 3 × 3 submatrices. The energy levels can still be obtained to any desired degree of accuracy by trial numerical substitution; quite satisfactory agreement with the spectrum of the vinyl grouping in styrene (X) was obtained (39) with the following parameters



(X)

$\delta_A = 0$ p.p.m. $\quad J_{AB} = 1.2$ c.p.s.

$\delta_B = -0.25$ p.p.m. $\quad J_{AC} = 11.3$ c.p.s.

$\delta_C = -1.50$ p.p.m. $\quad J_{BC} = 17.8$ c.p.s.

Similar agreement was found in an analysis of the *ABC* spectra of 2,4-dichloroaniline and 2,5-dichloroaniline (39).

In the case of the system *ABX*, where it is assumed that the *X* signal is well separated from the *AB* region, certain off-diagonal elements become very small relative to the diagonal terms; when they are neglected, matrix diagonalization reduces to the solution of quadratic equations and the energy levels are readily expressed in explicit analytical form (37,40). The system *ABX* gives rise to 14 lines, of which four can be considered *A* transitions, four *B* transitions, four *X* transitions, and two weak combination lines. Spectra of this type are most readily interpreted if we consider J_{AX} and J_{BX} as perturbations of the *AB* and *X* resonances. Each of the four lines in

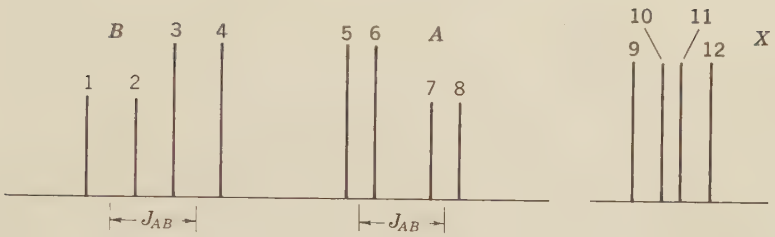


Fig. 11. *ABX* spectrum.

the *AB* spectrum is split into a doublet (Fig. 11); the two *B* lines are both split by

$$\nu_2 - \nu_1 = \nu_4 - \nu_3 = {}^1/_2(J_{AX} + J_{BX}) + C_{ABX}$$

and the two *A* lines by

$$\nu_8 - \nu_7 = \nu_6 - \nu_5 = {}^1/_2(J_{AX} + J_{BX}) + C_{ABX}$$

where C_{ABX} is a quadratic function of $\delta_{\nu(AB)}$, J_{AB}, J_{AX}, and J_{BX} and has the value zero when $J_{AX} = J_{BX}$. The *X* spectrum is a symmetrical quadruplet with splittings equal to those just given for the *AB* resonance

$$\nu_{12} - \nu_{11} = \nu_{10} - \nu_9 = \nu_8 - \nu_7 = \nu_6 - \nu_5$$

$$\nu_{11} - \nu_9 = \nu_{12} - \nu_{10} = \nu_2 - \nu_1 = \nu_4 - \nu_3$$

If $\delta_{\nu(AB)}$ is small enough, the *A* and *B* quadruplets may overlap. Explicit formulas for all 14 transition energies and line intensities are given by Bernstein, Pople, and Schneider (37); satisfactory agreement between the calculated and observed *ABX* ring proton spectra of 2,3-lutidine was obtained.

The *ABC* spectrum contains the same 12 lines which are strong in the *ABX* spectrum, while a third combination line, forbidden in the *ABX* case, appears to give a total of 15 transitions.

G. THE FOUR-PROTON SYSTEMS A_2B_2 AND A_2X_2

The complete matrix for the system of two pairs of two equivalent nuclei has been evaluated (38,66); it is assumed at the outset that $J_{AB} = J_{A'B'}$ and that $J_{A'B} = J_{AB'}$ by symmetry. There are 4

weak combination transitions and 24 transitions which can be classified as either A or B. The set of 12 A-lines is always the mirror image of the set of 12 B-lines about the central position. The symmetry of the A_2B_2 and A_2X_2 spectra should be of considerable help in their identification. In the case of A_2B_2, 6 of the 12 A-lines can be obtained directly from the matrix, but the other 6 require the solution of a fourth order determinant. In the case of the A_2X_2 system, where the appropriate, relatively small, off-diagonal elements can be neglected, the problem again reduces to the solution of quadratics and the energies and intensities of all 24 transitions can be obtained explicitly (66).

The appearance of the A_2B_2 spectrum varies widely with different sets of coupling constants. The simplest spectrum occurs when the AB coupling constants are equal ($J_{AB} = J_{A'B}$). If, also, the chemical shift is large as in A_2X_2, some transitions are forbidden and many of those remaining are degenerate, so the spectrum consists of two 1–2–1 triplets (cf. Section IV-B). The separation between the components of each triplet is equal to J_{AB}; the spectrum is independent of $J_{AA'}$ and $J_{BB'}$. When δ_ν/J_{AB} is decreased, each triplet breaks up into a 7 line multiplet (Fig. 12), the complete 14 line spectrum still being symmetrical about the midpoint. Lines 5 and 10 (Fig. 12), give directly the chemically shifted but spin-spin unperturbed resonance positions of the two nuclei.

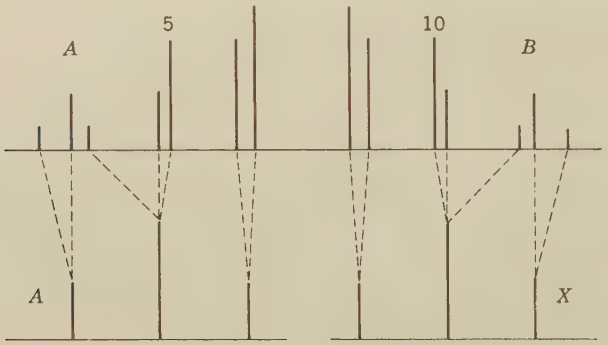


Fig. 12. A_2B_2 spectrum when $J_{AB} = J_{A'B}$ (*upper*) and A_2X_2 spectrum when $J_{AB} = J_{A'B}$ (*lower*).

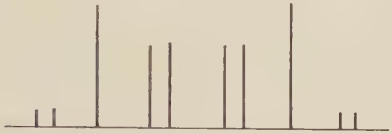


Fig. 13. A-half of A_2X_2 spectrum when $J_{AB} = J_{A'B}$ and $J_{AA} > J_{BB} > 0$.

When $J_{AB} \neq J_{A'B}$ and $J_{AA} > J_{BB} > 0$ the A-half of the A_2X_2 spectrum (Fig. 13) has 10 lines in a symmetrical pattern; the 2 intense lines are doubly degenerate and the X-half is identical with the A-half. Under the same conditions the A_2B_2 spectrum contains all 24 lines. Unlike spectra discussed previously, these depend on coupling constants between structurally equivalent protons (J_{AA} and J_{BB} or J_{XX}). This dependence arises because the states of group A_2 where $M = 0$ are no longer pure singlet or triplet (cf. Section IV-B) since the two A protons are coupled unequally to the B protons. Transitions otherwise forbidden are therefore allowed. Spectra of this type were observed and analyzed in the cases of 1,1-difluoroethylene (38), 1,2-chlorobromoethane (66), 1,2-dichlorobenzene (66), and naphthalene (66).

H. OTHER SPIN-COUPLED SYSTEMS

The four proton system AB_3, exemplified by methyl mercaptan, has been analyzed by Abraham, Pople, and Bernstein (67). The 110 line AB_2X_2 spectrum of pyridine or a monosubstituted benzene has been treated by Schneider, Bernstein, and Pople (36). The spectrum calculated for A_2B_6 (68) agreed with that found for propane when $\delta_{AB} = 0.438$ p.p.m. and $J_{AB} = 7.26$ c.p.s. An analysis of $X_3AA'X_3'$ with $J_{XX} = 0$, $J_{AX} = J_{A'X'} \neq J_{AX'} = J_{A'X}$, as in isobutylene, has been done by Naar-Colin and Bothner-By (69). Several complex systems have been treated by Gutowsky *et al.* (60).

I. MULTIPLET MOMENT THEOREMS

Derived from the Hamiltonian by Anderson and McConnell (72), these are useful in the further analysis of spin-spin multiplets. The complete multiplet, ν_a, ν_b, ν_c, ν_d, . . ., generated by any isolated N proton system ABC. . ., will have a *first moment*

$$M_1 = \sum_a (\nu_a - \nu)R_a$$

about a frequency ν. R_a, R_b, . . ., are the intensities of the respec-

tive peaks, given by the areas under the absorption signals. The first moment is zero about a frequency $\nu = \nu_0$ when

$$M_1 = 0 = \sum_a (\nu_a - \nu_0) R_a$$

The mean, or center of gravity, ν_0, of the multiplet is independent of J_{AB}, J_{AC}, J_{BC}, . . ., but determined by the chemically shifted but otherwise unperturbed frequencies ν_A, ν_B, ν_C, which the protons would generate if they were not coupled

$$\nu_0 = 1/N \sum_A \nu_A$$

where the total intensity has been normalized to the number, N, of protons present in the system, i.e., $R_A = R_B = R_C = 1$.

The complete multiplet ν_a, ν_b, ν_c, . . ., generated by any isolated N proton system ABC. . ., will have a *second moment* about ν_0

$$M_2 = \sum_a (\nu_a - \nu_0)^2 R_a$$

which is independent of all J coupling but determined by the unperturbed frequencies ν_A, ν_B, ν_C, . . .

$$M_2 = \sum_A (\delta_{0A})^2$$

where δ_{0A} is the separation of ν_A from the center of gravity, ν_0, and the total intensity has again been equated with N. When there are only two different kinds of protons, A and B, the second moment is simply related to δ_{AB}. Thus, for A_nB_m

$$M_2 = (nm/N)(\delta_{AB})^2$$

The *third moment*

$$M_3 = \sum_a (\nu_a - \nu_0)^3 R_a$$

is also independent of J coupling. The *fourth moment* is dependent upon J coupling and may be used in some instances for the calculation of the coupling constant (72).

J. CORRELATION OF COUPLING CONSTANT WITH STRUCTURE

The relevant data have only begun to be collected, but there is already considerable evidence that J-values are characteristically dependent upon structure and it is clear that they will be comparable

in importance to chemical shift parameters in the analysis of unknown structures. A weak correlation between coupling and the electronegativity of attached groups has been noted (71). The first rule of thumb to emerge is the rapid decrease of J_{HH} with an increase in the number of chemical bonds separating the protons; this is quite reasonable in view of the mechanism assumed for the coupling (see Section IV-A). J for two nonequivalent geminal protons in a saturated methylene group CH_AH_B is usually in the range 12–15 c.p.s., whereas J for two protons attached vicinally as in H_A—C—C—H_B is usually in the range 0–12 c.p.s. Coupling between protons separated by more than two other saturated atoms is usually exceedingly small (<1 c.p.s.). Similar monotonic attenuation of J occurs in unsaturated or aromatic systems; for example, the coupling, J_o, between *ortho* hydrogens on an aromatic ring was found to be 7.9 c.p.s.; average *meta* coupling, J_m, is 2.1 c.p.s.; and *para* coupling, J_p, is 0.5 c.p.s. (40).

Fluorine-fluorine coupling, however, does not appear to obey this simple rule, with $J_{FF(o)} = 20.5$, $J_{FF(m)} = 3.1$, and $J_{FF(p)} = 13.2$ c.p.s. (40); similar exceptional behavior was noted in other cases (56). Hydrogen-fluorine coupling is also sometimes exceptional (57).

Superimposed on the downward trend of J_{HH} with increasing numbers of intervening bonds are certain specific effects associated with the stereochemistry. Analysis of spectra of the acetyl derivatives of glucose, galactose, xylose, and arabinose showed that the spin coupling between hydrogens on neighboring carbon atoms is two to three times greater when both hydrogens are in axial orientation than it is when one or both of the hydrogens are in equatorial orientation (19). In agreement with this, the proton spectrum of C^{13}-dioxane (the isotope is present in 1% natural abundance) was interpreted on the basis of the A_2X_2 model where the coupling constants J_{ae} and J_{ee} for the *gauche* conformations both have the value of 2.7 ± 0.2 c.p.s., whereas that (J_{aa}) for the *trans* diaxial coupling is 9.4 ± 0.2 c.p.s. (59). In this computation allowance must be made for the fact that a given pair of vicinal hydrogens spends an equal time in each of two conformations, so that the average values, $J_{cis} = {}^1/_2(J_{ae} + J_{ea})$ and $J_{trans} = {}^1/_2(J_{aa} + J_{ee})$, will apply. Similar considerations hold for vicinal olefinic protons; the *trans* pair in the vinyl group of styrene (X) are coupled by $J = 17.8$ c.p.s., whereas J for the *cis* pair is 11.3 c.p.s. (39), and a study (60) of a number of

simple disubstituted olefins of known configuration has established $J_{trans} > J_{cis} > J_{gem}$ as regular behavior.

Spin coupling between protons involves magnetic polarization of the intervening electron cloud, as pointed out in Section IV-A. The proton-electron interactions have several different mechanisms (Ramsey, 52), involving the magnetic moments associated with both electronic orbital motion and electron spin, but only one of these appears to be sufficiently important to account for the magnitude of the observed couplings; this operates through the electron spin and is known as the Fermi or contact interaction since it depends upon the electron spin densities at the protons. The value of the coupling constant can be calculated by a second order perturbation treatment (52) which introduces triplet excited states into the molecular electronic wave function, or by a further approximation using an average excitation energy, directly from the ground state wave function; this was done by Ramsey in the case of molecular hydrogen with the James-Coolidge function. A Heitler-London product of atomic orbitals has been used (33) and a number of valence bond approximations have been reported by Karplus and his associates (61,62,119); these lead to a theoretical value of 10.4 ± 1.0 c.p.s. for the coupling in methane, to be compared with a value of 12.4 ± 1.6 c.p.s. estimated from the splitting in CH_3D. Moreover, the J between protons within a methylene grouping (61) is predicted to be a sensitive function of the H—C—H bond angle, such that J decreases from a value of perhaps 20 c.p.s. at a bond angle of 105 degrees to zero when the angle is widened to about 125 degrees; wider angles than this are expected to give small negative values of J. The number of molecules for which the H—C—H bond angle is accurately known is quite limited, but those available give good agreement with the calculated curve. In particular, the two geminal hydrogens of a vinylidene grouping, $>C{=}CH_2$, are predicted to be very weakly coupled ($J \cong 1$ c.p.s.) since the central carbon is sp^2 hybridized and the H—C—H angle is large, and coupling constants as small as this are indeed observed.

Karplus' valence bond calculation (119) of contact coupling of two vicinal protons, as in ethane, predicts the interesting result that $J_{HH'}$ will depend in a sensitive fashion upon the angle ϕ between the H—C—C′ and C—C′—H′ planes, such that coupling is maximal at dihedral angles of 0 and 180 degrees and minimal (zero or less) at a dihedral angle of about 90 degrees; the magnitude of $J_{HH'}$ at the 180

degrees maximum was calculated as 9.2 c.p.s., somewhat larger than that (8.0 c.p.s.) at $\phi = 0$ degrees.

Parallel calculations of the vicinal proton coupling constant, employing a molecular orbital method, have been carried out by the present author (120); these were based upon McConnell's general approximation (63) derived in turn from Ramsey's equation (52) with the use of an antisymmetrized (determinantal) electronic wave

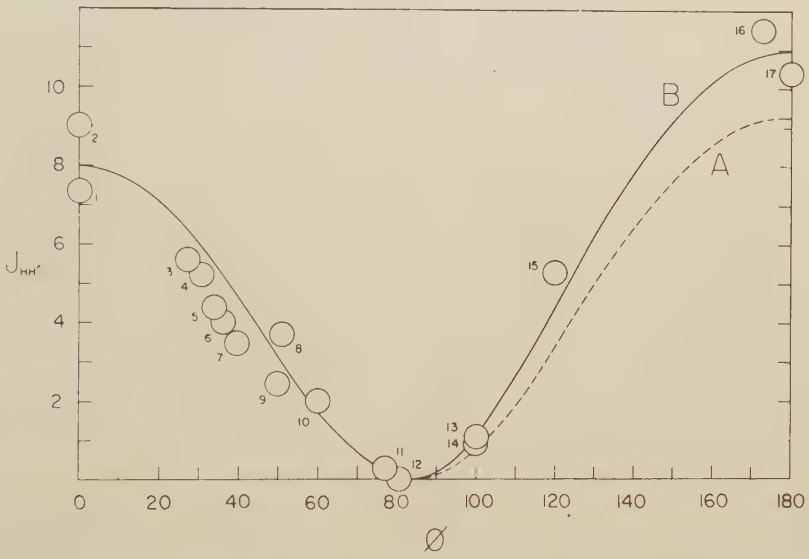


Fig. 14. Theoretical curve and experimental points showing the variation of coupling constant with the dihedral angle ϕ in the saturated system H—C—C—H (120).

function. It was shown that the major contribution to coupling is proportional to the square of the overlap integral between the two vicinal C—H bond orbitals. These results are summarized in the theoretical curve (*B*, Fig. 14). There is good agreement with a number of new experimental points derived from the high resolution spectra of substances whose molecular structures fall in the class of rigid, caged systems, each containing one or more pairs of nonequivalent vicinal tertiary protons for which the relevant dihedral angles could be reliably estimated from models.

V. Kinetic Effects

A. PROTON RESIDENCE TIMES

In many systems the protons are not all firmly attached at given sites upon a rigid molecular framework. Proton motion with respect to a set of molecular coordinates may be classified as involving (*1*) internal reorientation of molecular groupings, i.e., conformational changes, and (*2*) intra- or intermolecular proton exchange (cf. ref. 80). The general problem has been treated by Gutowsky, McCall, and Slichter (33), Gutowsky and Saika (73), and Gutowsky and Holm (74). If protons are moving between two environments A and B they will have average residence times τ_A and τ_B at each site, given by

$$\tau_A = 1/k_A \qquad \text{and} \qquad \tau_B = 1/k_B$$

where k_A and k_B are the first order rate constants for the exchange between sites. Generally the shielding constant σ for protons at site A will differ from that for protons at B; there will be a chemical shift δ_ν between protons in the two environments. If the residence times are sufficiently short, only a single absorption line will be observed at a position corresponding to the weighted average of the resonant frequencies which would have been generated had the protons been confined.

In the case where the populations at both sites are equal, when $\tau_A = \tau_B = \tau$, this condition is met if $\tau\delta_\nu \leqslant \sqrt{2}$. But if the residence time is longer or the chemical shift is larger, such that $\tau\delta_\nu > \sqrt{2}$, separate resonance lines will be seen with an experimentally observed shift, $\delta_{\nu(e)}$, given by

$$\delta_{\nu(e)} = \delta_\nu \left[1 - 2/(\tau\delta_\nu)^2\right]^{1/2}$$

Measurement of $\delta_{\nu(e)}$, and hence τ, the residence time, as a function of temperature allows the calculation of Arrhenius activation energies and frequency factors in the usual manner.

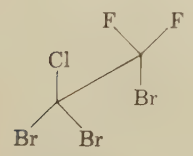
B. KINETICS OF CONFORMATIONAL CHANGES

A straightforward illustration of the effect of varying residence times was provided by Bottini and Roberts (75); in the case of *N*-ethylethyleneimine, with the position of the ethyl fixed in relation to the ring, the two ring protons *cis* to ethyl have a chemical shift

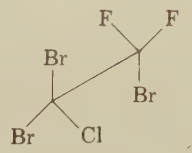
different from that of the *trans* protons. The spectrum at room temperature shows two slightly split triplet band systems for the ring protons, characteristic of an incompletely resolved A_2B_2 absorption pattern. The triplets are separated by 27 c.p.s. at 40 Mc., which means that the mean lifetime of a given imine molecule before the nitrogen inverts must be much greater than 0.04 sec. On heating to 120–130° the ring hydrogens lose their identity with respect to the position of the ethyl group and the mean lifetime must be substantially less than 0.04 sec.; the triplets collapse to a single peak at a central position at about 110°.

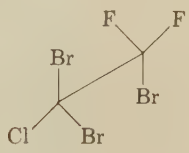
The question of internal rotation has been discussed by Gutowsky and Holm (74) and by Phillips and co-workers (76–78). A rotational barrier of 7 ± 3 kcal./mole for the amide linkage in dimethylformamide is responsible for the presence of two methyl resonance lines in the spectrum measured at room temperature. The temperature dependence of the spectrum of dimethylnitrosamine, which similarly shows two lines at 25° but only one line at temperatures >ca. 180°, yields a value of 23 kcal./mole for the rotational barrier. Barriers in alkyl nitrites have also been obtained, as well as the isomer ratios for a series of aldoximes whose *syn* and *anti* isomers are in equilibrium.

In the case of substituted ethanes the barrier for rotation about the central C—C bond is expected to be small. At ordinary temperatures the residence time in each of the three conformations is generally sufficiently short so that only an average spectrum is observed, but at low temperatures the individual conformers may contribute their own peaks to the spectrum (76,78,79). Thus at −80°, the ethane $CBrF_2$—CBr_2Cl appears to "freeze" to about a 1.4:1 mixture of the symmetrical form (XI), identified by its single F^{19} line, and the *d,l* pair (XII), identified by its F^{19} nonequivalence quadruplet (79). Al-



(XI)





(XII)

though with rapidly rotating ethanes the chemical shift between geminal nuclei is averaged, it is not necessarily averaged to zero unless the residence times in each of two mirror image conformations

(with nonzero geminal shift) are equal. For example, the geminal fluorines in $CBrF_2$—$CHBrCl$ are nonequivalent in chemical shift at temperatures up to 200° (76,79), although the degree of nonequivalence varies with temperature because the relative residence times are temperature dependent. Similarly (79), the methylene group of 2,3-dibromo-2-methylpropionic ester gave a resonance quadruplet while the more symmetrical derivative, 1,2-dibromo-2-methylpropane, showed a single sharp methylene line. It is significant, moreover, that even in cases where geminal protons become equivalent in chemical shift, through rotational averaging, they are not necessarily equally spin-coupled to adjacent protons; the high resolution A_2B_2 spectrum of 1,2-chlorobromoethane (66) can be adequately interpreted only on the basis that $J_{AB} \neq J_{A'B}$.

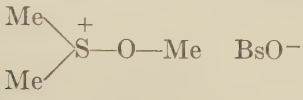
VI. Applications to Structural Problems

Certain classes of model substances have been studied with a view toward empirical correlations useful in the determination of unknowns. The *cis* and *trans* forms of decalin and their derivatives can be distinguished (83); the flexible *cis*-locked compounds give a relatively sharp ring proton resonance, whereas the more rigid *trans*-decalins, with protons of fixed type (axial or equatorial, whose shieldings will generally differ) show broader and more complex spectra. Cyclohexane itself gives a single sharp line, the result of the rapid chair-chair interconversion, which averages any axial-equatorial shift to zero. The spectra of a number of cyclohexanone, indanone, and camphor derivatives and the factors influencing some of the chemical shifts therein have been discussed (84). The NMR spectra of 47 steroids were obtained and a number of peak positions measured by Shoolery and Rogers (20); empirical correlations allowed the assignment of characteristic group frequency shifts to a number of functional groups. In the steroids, axial protons in the 3- and 11-positions were found to be shifted apart from the corresponding equatorial protons by about 0.5 p.p.m.

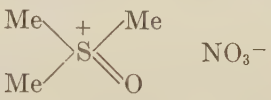
The proton spectra of azulene and acepleiadylene, measured under conditions of high resolution, were analyzed in detail and the chemical shifts and coupling constants were evaluated and discussed in terms of the ring current model (85). NMR has been shown useful in the determination of the extent of substitution at the α- and β-positions of the indole nucleus (86). Furan shows two triplets, with $J = 1.5$

c.p.s., with the α-hydrogens appearing at a lower field than that of the β-hydrogens; this trend, consistently borne out in a number of substituted furans as well, was used in confirmation of appropriate structural assignments in the naturally occurring complex furan derivatives, cafestol, columbin, and limonin (87).

Many structural applications of NMR have involved nothing more complicated than a determination of the number of peaks and their relative areas. Thus Smith and Winstein (88) were able to distinguish between two kinds of dimethyl sulfoxide adducts; the compound (XIII) produced from dimethylsulfoxide and methyl *p*-bromobenzenesulfonate showed three resonance peaks, in area

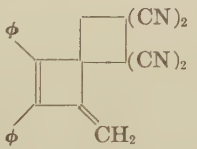


(XIII)



(XIV)

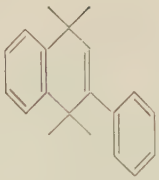
ratio 4:3:6, due respectively to the aromatic, *O*-methyl, and *S*-methyl protons, whereas the compound (XIV) formed from dimethyl sulfoxide and methyl nitrate showed only a single peak due to the nine fully equivalent methyl protons. The diamagnetic complex $C_8H_8Fe(CO)_3$ from cyclooctatetraene and iron pentacarbonyl shows a single proton resonance (89), as does cyclooctatetraene itself, which implies that no four carbon atoms in the C_8H_8 moiety of the complex are preferentially bonded to the metal atom, but that all eight atoms are equivalently bonded and that the ring is planar, or nearly planar,



(XV)

in the complex. The adduct (XV) from 1,2-diphenyl-3,4-dimethylenecyclobutene and tetracyanoethylene gives three peaks with approximate area ratio 5:1:1 and at the expected positions for aromatic, exomethylene, and saturated ring methylene protons (90). The structure of the hydrocarbon produced in the reaction of 2,5-diacetoxy-2,5-dimethyl-3-hexyne with benzene in the presence of aluminum chloride was shown to be XVI, not XVII, since the product gave no

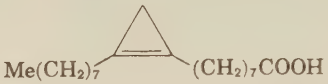
(XVI)



(XVII)

olefinic proton absorption (91). No olefinic proton peak, but other absorption consistent with structure XVIII, was found in the spec-

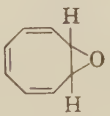
(XIX)



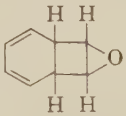
(XVIII)

(XX)

trum of sterculic acid, with the effective exclusion of the alternatives (XIX and XX) (92). Cyclooctatetraene oxide (93) shows two peaks of area ratio 3:1, as expected for the six olefinic and two aliphatic protons of XXI but not for the tricyclic alternative (XXII). The

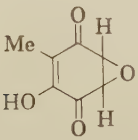


(XXI)

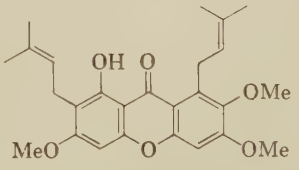


(XXII)

spectrum of terreic acid (XXIII) contains three peaks of the intensity ratio 3:2:1 at the expected positions for methyl, oxirane, and hydroxyl protons; the chemical shift of the oxirane proton is similar to that exhibited in the model, 2,3-epoxy-1,4-naphthoquinone (94). NMR



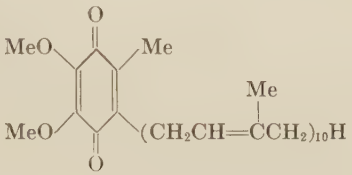
(XXIII)



(XXIV)

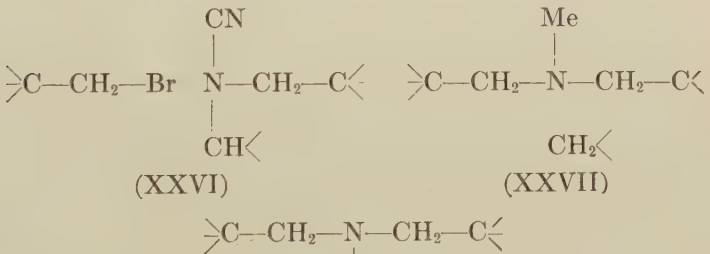
evidence was used by Yates and Stout (95), in a proof of the structure of mangostin; the ratio of the areas of the *C*-methyl and *O*-methyl peaks in the spectrum of dimethylmangostin (XXIV) was found to be 1.33–1.40, and since three methoxyl groups were known to be present in this derivative the presence of four *C*-methyls was corroborated.

The spectrum of the ozonolysis product of XXIV showed that all of the *C*-methyl groups had been lost and so confirmed the presence of the two isopentenyl side chains. Similarly, NMR helped provide evidence for two methoxyls, one *C*-methyl, and one isoprenoid chain of 10 units attached to a benzoquinone nucleus in coenzyme Q_{10} (XXV) (96) and excluded the presence of aromatic protons, terminal methylene, and ethyl groups.



(XXV)

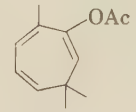
The alkaloid aspidospermine and a number of its degradation products have been studied with the aid of NMR (97); the von Braun bromocyanamide (part structure XXVI) gave two absorption peaks of area corresponding to two protons each and identified with the $—CH_2NCN$ and $—CH_2Br$ systems. The bromomethyl peak was replaced by new *C*-methyl absorption upon reductive debromination. The Emde base (part structure XXVII) prepared from aspidospermine methiodide with sodium–liquid ammonia gave additional CCH_2C absorption but no new *C*-methyl peak; these results led to the conclusion—which was later confirmed by chemical evidence—that aspidospermine contains the grouping XXVIII.



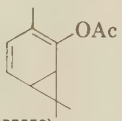
(XXVI) (XXVII) (XXVIII)

Corey, Burke, and Remers (98) found that the enol acetate of eucarvone is a cycloheptatriene (XXIX) rather than a caradiene

(XXX) since the spectrum contains olefinic and *gem*-dimethyl ab-



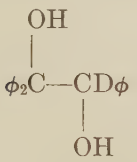
(XXIX)



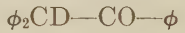
(XXX)

sorption in a 4:6 intensity ratio as well as two singlet peaks for allylic methyl and *O*-acetyl groups, but no peaks which might be ascribed to two tertiary bridge hydrogens. The bicylic valence tautomeric structures were also excluded for cycloheptatriene itself, 1,1,4-trimethylcycloheptatriene, and 1,1,3,4-tetramethylcycloheptatriene by similar observations. A related study by Doering *et al.* (99), deals with the formulas of the cycloheptatriene carboxylic acids (Buchner acids).

The benzhydryl phenyl ketone (XXXII) resulting from the acid-catalyzed pinacol rearrangement-dehydration of deuterated 1,1,2-triphenylethylene glycol (XXXI) was found still to contain deuterium since its spectrum does not contain the resonance peak due to the tertiary hydrogen present in an authentic unlabelled benzhydryl



(XXXI)



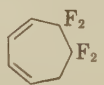
(XXXII)

phenyl ketone sample (100). Exchange of deuterium with D_2O occurs in the 4- and 5-positions of glyoxaline (101), whereas with sodium deuteroxide it occurs initially in the 2-position as shown by the NMR spectra of the deuterated products in each case.

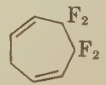
The proton and fluorine spectra provided support for structures XXXIII and XXXIV for the 1:1 adducts of cyclopentadiene and tetrafluoroethylene as well as for structures XXXV and XXXVI

(XXXIII)

(XXXIV)



(XXXV)

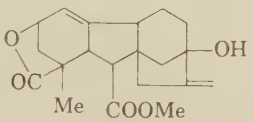


(XXXVI)

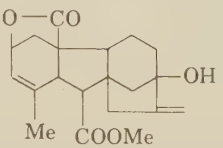
assigned to the products formed on thermal rearrangement of these materials (102). Structure XXXVII for the dimer of tetrafluoroallene was confirmed by fluorine resonance techniques (103).

(XXXVII)

The methyl ester of gibberellic acid shows a peak of the correct intensity, shift, and sharpness to be attributed to a methyl group attached to a saturated quaternary carbon atom, as in XXXVIII (104); there are no neighboring hydrogen atoms to broaden the line by spin-spin coupling. The absence of the MeC=C group of the alternative formula (XXXIX) is indicated by a lack of a similar sharp peak at the lower field characteristic of the allylic methyl.

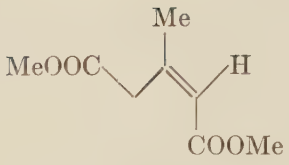


(XXXVIII)

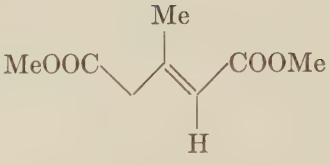


(XXXIX)

Several interesting studies have utilized a "*cis* effect" in evidence in the case of α,β-unsaturated carbonyl compounds. The proton grouping substituted upon the β-carbon *cis*, for example, to a carbomethoxyl group appears at fields lower than does the corresponding *trans* function. With dimethyl citraconate, dimethyl mesaconate, dimethyl maleate, and dimethyl fumarate, etc., this β-*cis* shift amounts to 0.15–0.25 p.p.m. for methyl and 0.5–0.75 p.p.m. for olefinic protons (105). The acid, m. p. 115–116°, commonly accepted in the literature as *trans*-β-methylglutaconic acid was seen to be a mixture of the *cis* and *trans* isomers (105), since the methyl ester gives the four resonance lines of the *cis* derivative (XL) at +4.83 (*C*-methyl), +3.15 (*O*-methyl), +3.03 (methylene), and +0.98 (olefinic) (p.p.m. versus ext. toluene aromatic) as well as two additional lines due to the *trans* ester (XLI). The pure dimethyl *trans*-β-methylglutaconate shows peaks at +4.60 (*C*-methyl), +3.58 (methylene), +3.15 (*O*-methyl), and +1.00 (olefinic). The same effect was noted (106)



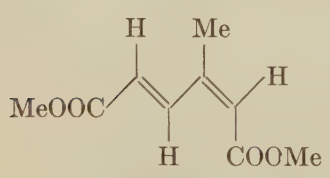
(XL)



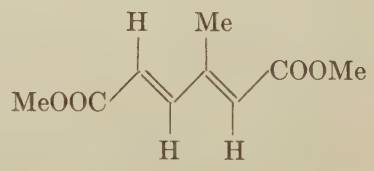
(XLI)

with the *C*-methyl resonance in ethyl β-chlorocrotonate, which occurs at lower field in the stereoisomer with the *cis* relation between the *C*-methyl and carboethoxyl groups. These chlorocrotonates undergo bimolecular displacement of the halogen with the nucleophiles EtS^- and ϕS^-, and the nucleophilic substitutions were shown to proceed with retention of configuration since the product from the ethyl *cis*-β-chlorocrotonate gives a *C*-methyl resonance peak at lower field than that of the thioether from the *trans* ester. The origin of the *cis* shift was suggested (106) to be weak hydrogen bonding between the hydrogen of the methyl group and the carbonyl oxygen (a more tenable hypothesis would invoke the magnetic anisotropy of the neighboring carbonyl (cf. Section III-D)).

A related study (107) involved the lower melting form of β-methylmuconic acid (m.p. ca. 170°) whose dimethyl ester was shown to be XLII. The *C*-methyl appears at +4.43 or 0.25 p.p.m. higher than the *C*-methyl in XLIII, the *trans-trans* derivative of known configuration, whereas that peak should have been lower if the *C*-methyl and carbomethoxyl groups had been *cis*. That the other double bond in XLII is *trans* was deduced from the magnitude of *J* (16 c.p.s.) for the γ,δ-olefinic proton nonequivalence quartet; the corresponding *J* for the known XLIII is 15.5 c.p.s., as expected for *trans* coupling of olefinic protons but too large for *cis* coupling (Section IV-J). Moreover one of the olefin doublets had dropped from its position at −0.83 in the spectrum of XLIII to −2.10 in that of XLII, consistent



(XLII)



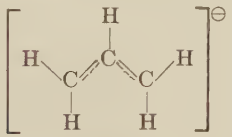
(XLIII)

with the proximity of the γ-proton to both carbomethoxyls in the latter ester.

Spin-spin splitting patterns have yielded much valuable structural information. The proton spectrum of allyl magnesium bromide is of AX_4 type (Section IV-B), reasonably interpretable only if the equilibrium

$$BrMgCH_2CH{=}CH_2 \rightleftharpoons CH_2{=}CHCH_2MgBr$$

is assumed to be very rapid, with residence time $<<0.01$ sec., but still long enough to permit each form rotation about its 1,2-C—C bond (108). Thus there is no differentiation between *cis*- and *trans*-hydrogens as would have been expected for a symmetrical, completely ionic structure, such as XLIV, or a symmetrical bridged structure with double coordination by magnesium as in XLV.

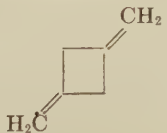


(XLIV)

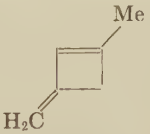
(XLV)

In another investigation of organometallics, β-methoxyethylmercury(II) acetate and β-hydroxyethylmercury(II) hydroxide were found to give rise to A_2X_2 spectra (two triplets) for the two methylenes in each case (109).

1,3-Dimethylenecyclobutane (XLVI) and its isomer, 1-methyl-3-methylenecyclobutene (XLVII) were readily distinguished (110);

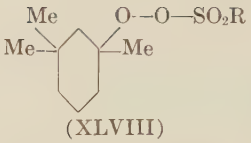


(XLVI)

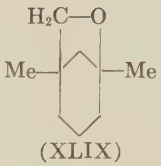


(XLVII)

the former showed two principal groups of resonance lines each having five components (A_4X_4 system) at +2.38 and +3.75 (p.p.m. versus ext. benzene), whereas the latter showed the expected olefinic proton, methylene, and allylic *C*-methyl peaks with intensities roughly proportional to the numbers of hydrogens involved. The product (XLIX) of the heterolytic decomposition of 1,3,3-trimethylcyclohexyl hydroperoxide *p*-nitrobenzenesulfonate (XLVIII) was identified

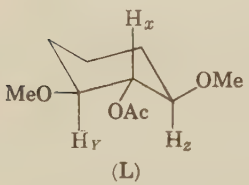


(XLVIII)

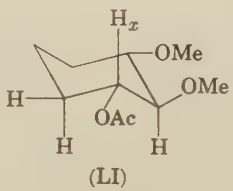


(XLIX)

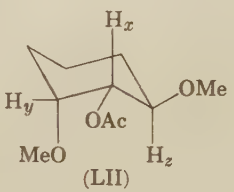
(111) by the quartet centered at +1.20 due to —CH_2O, two methyl peaks at +3.45 and +3.65 and a peak from the remaining eight protons at +3.23 (p.p.m. versus ext. water). The product resulting from methoxide ion methanolysis of 3-methoxycyclohexane α-oxide was shown to be L rather than LI (after acetylation), since the H_x in the acetate shows a 1:2:1 triplet at +2.88 (p.p.m. versus internal chloroform). The H_x is equally coupled by a relatively large J (ca. 9 c.p.s.) to two vicinal protons, H_y and H_z, both of which must therefore maintain a *trans*, diaxial relationship with H_x. The corresponding acetylated product from the β-oxide has the configuration LII where H_x gives rise to a symmetrical quartet at +2.80 with splittings of 3 and 9 c. p. s., as expected when H_x is coupled to one equatorial and to one axial hydrogen (Section IV-J) (112).



(L)

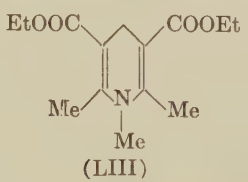


(LI)

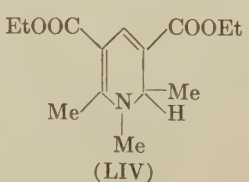


(LII)

Diethyl 1,4-dihydro-1,2,6-trimethylpyridine-3,5-dicarboxylate (LIII) was shown to be that and not the 1,2-dihydro derivative (113). The spectrum shows five main resonances: (*1*) a quartet at −0.60 (two ethyl methylenes), (*2*) a singlet at +1.17 (*N*-methyl), (*3*) a singlet at +1.35 (ring methylene), (*4*) a singlet at +2.60 (two ring *C*-methyls), and (*5*) a triplet at +4.60 (two ethyl *C*-methyls) (p.p.m. versus ext. water). The presence of the ring methylene and two



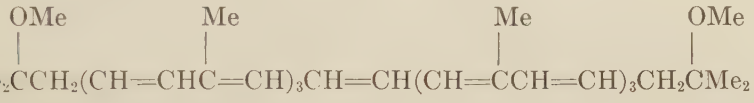
(LIII)



(LIV)

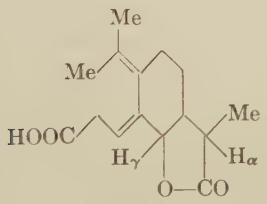
equivalent ring *C*-methyl groups eliminates the alternative (LIV).

Spirilloxanthin (LV) (114) shows bands at τ = 6.78 (*O*-methyl), 7.70 (methylene doublet; J = 6.8 c.p.s.), 8.02 (allylic *C*-methyl), and 8.83 (*gem*-dimethyl).

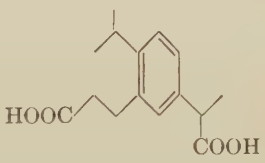


(LV)

Photosantonic acid (LVI) (115) shows a methyl doublet at +5.34 (p.p.m. versus ext. benzene) for the lactone methyl group, split by the single proton at the α-position on the lactone ring. The two other methyl groups, which are allylic and nonequivalent, appear at +4.67 and +4.84. There is a doublet at +3.47 and +3.60 associated with the methylene located between two unsaturated carbons (the carboxyl and the β-carbon in the side chain) and another doublet at +2.47 for the γ-proton on the lactone ring, coupled to its neighbor. The olefinic proton adjacent to the side chain methylene appears as a 1:2:1 triplet at +0.92. Particularly interesting is the evidence for coupling through *four* bonds in the system HC=CCH. Each member of the olefinic triplet is further split into a close doublet by the allylic γ-proton (another case of such 1,3-coupling was seen with 1,3-dimethylenecyclobutane (XLVI)). The aromatic dehydrophotosantonic acid (LVII) shows the expected two *gem*-*C*-methyls, which are



(LVI)

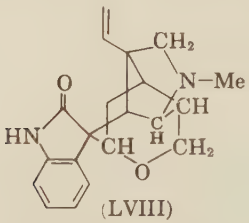


(LVII)

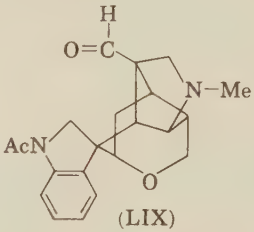
now rendered equivalent in chemical shift by rotational averaging but split by the adjacent benzylic proton, and another methyl doublet at a lower field which is split by the other benzylic proton; the remaining aliphatic absorption shows the integrated intensity expected of four protons.

The vinyl group of gelsemine (LVIII) (116) gives an isolated *ABC* spectrum with three symmetrically split quartets centered at values of

τ = 3.72, 4.95, and 5.10 and with splittings of 17.8, 11.3, and 1.5



(LVIII)



(LIX)

c.p.s., corresponding to *trans*, *cis*, and geminal couplings, respectively, within the vinyl function. The absence of any further splitting in the low field set, i.e., the isolation from further coupling to a fourth proton indicates that the gelsemine vinyl group is attached to a quaternary carbon atom. This was borne out by the spectrum of the aldehyde (LIX) prepared by degradation, which contains none of the peaks ascribed to the vinyl, but instead a sharp singlet CCHO resonance line at τ = 0.11. The presence of the system $\begin{matrix} & & C & \\ & & | & \\ C & C & CH_2 & NMe \\ & & | & \\ & & C & \end{matrix}$ in LVIII was confirmed by the discrete nonequivalence quartet centered at τ = 7.55 with J = 10.6 c.p.s. and by the *N*-methyl singlet at 7.84. The *O*-methylene, adjacent to one proton, appears as an octet centered near 6.10, the AB segment of an ABX spectrum. The octet splittings, 11.5, 1.6, and 0.9 c. p. s., correspond respectively to the geminal methylene coupling and to the two different vicinal couplings. The OCH$\langle$ and NCH$\langle$ methine protons give multiplets at 6.25 and 6.60, respectively; from the fine structure actually resolved it was possible to deduce the minimum number of vicinal protons, as in $OCH\langle^{C}_{CH_2}$ $\left(\text{or } OCH\langle^{CH}_{CH}\right)$ and $NCH\langle^{C}_{CH}$.

While this brief section has covered the majority of structural adaptations of proton resonance spectroscopy described in the published literature to April, 1959, it can be regarded as no more than an introduction to the possibilities of the technique. The method has suddenly taken hold, so that the number of new applications even now in process must well exceed the total of those already in print. Let the pace quicken!

References

1. W. D. Knight, *Phys. Rev.*, *76*, 1259 (1949).
2. N. F. Ramsey, *Phys. Rev.*, *86*, 243 (1952).
3. L. H. Meyer, A. Saika, and H. S. Gutowsky, *J. Am. Chem. Soc.*, *75*, 4567 (1953).
4. J. T. Arnold and M. G. Packard, *J. Chem. Phys.*, *19*, 1608 (1951).
5. E. R. Andrew, *Nuclear Magnetic Resonance*, Cambridge University Press, Cambridge, 1956: (a) p. 78; (b) pp. 152 ff.; (c) p. 118; (d) p. 12.
6. A. A. Bothner-By and R. E. Glick, *J. Chem. Phys.*, *26*, 1647 (1957); *26*, 1651 (1957); and unpublished work.
7. A. A. Bothner-By and R. E. Glick, *J. Am. Chem. Soc.*, *78*, 1071 (1956).
8. A. Saika and C. P. Slichter, *J. Chem. Phys.*, *22*, 26 (1954).
9. J. N. Shoolery, *J. Chem. Phys.*, *21*, 1899 (1953).
10. B. P. Dailey and J. N. Shoolery, *J. Am. Chem. Soc.*, *77*, 3977 (1955).
11. M. L. Huggins, *J. Am. Chem. Soc.*, *75*, 4123 (1953).
12. A. L. Allred and E. G. Rochow, *J. Am. Chem. Soc.*, *79*, 5361 (1957).
13. A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, *70*, 833 (1958).
14. A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, *80*, 1728 (1958).
15. H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Am. Chem. Soc.*, *74*, 4809 (1952); L. H. Meyer and H. S. Gutowsky, *J. Phys. Chem.*, *57*, 481 (1953).
16. R. W. Taft, Jr., *J. Am. Chem. Soc.*, *79*, 1045 (1957).
17. J. E. Wertz, *J. Phys. Chem.*, *61*, 51 (1957).
18. H. Conroy and B. Bonne, unpublished observations; B. Bonne, M.A. Thesis, Brandeis University, Waltham, Mass., 1957.
19. R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, *79*, 1005 (1957).
20. J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, *80*, 5121 (1958).
21. A. D. Cohen and C. Reid, *J. Chem. Phys.*, *25*, 790 (1956).
22. E. D. Becker, U. Liddel, and J. N. Shoolery, *J. Mol. Spec.*, *2*, 1 (1958).
23. W. C. Dickinson, *Phys. Rev.*, *81*, 717 (1951).
24. J. A. Pople, *J. Chem. Phys.*, *24*, 1111 (1956).
25. L. Pauling, *J. Chem. Phys.*, *4*, 673 (1936).
26. J. S. Waugh and R. W. Fessenden, *J. Am. Chem. Soc.*, *79*, 846 (1957).
27. H. Conroy and P. R. Brook, to be published.
28. H. M. McConnell, *J. Chem. Phys.*, *27*, 226 (1957).
30. J. A. Pople, *Proc. Roy. Soc.* (*London*), *A236*, 515 (1956); *A239*, 541, 550 (1957).
31. U. Liddel and N. F. Ramsey, *J. Chem. Phys.*, *19*, 1608 (1951).
32. N. F. Ramsey and E. M. Purcell, *Phys. Rev.*, *85*, 143 (1952).
33. H. S. Gutowsky, D. W. McCall, and C. P. Slichter, *J. Chem. Phys.*, *21*, 279 (1953).
34. E. L. Hahn and D. E. Maxwell, *Phys. Rev.*, *88*, 1070 (1952).
35. H. S. Gutowsky, *Ann. N. Y. Acad. Sci.*, *70*, 786 (1958).
36. W. G. Schneider, H. J. Bernstein, and J. A. Pople, *Can. J. Chem.*, *35*, 1487 (1957); *Ann. N. Y. Acad. Sci.*, *70*, 806 (1958).

37. H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can. J. Chem.*, *35*, 65 (1957).
38. H. M. McConnell, A. D. McLean, and C. A. Reilly, *J. Chem. Phys.*, *23*, 1152 (1955).
39. R. W. Fessenden and J. S. Waugh, 132nd Meeting, ACS, New York, September, 1957, *Abstr.*, p. 72P.
40. H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *J. Am. Chem. Soc.*, *79*, 4596 (1957); G. A. Williams and H. S. Gutowsky, *J. Chem. Phys.*, *25*, 1288 (1956).
41. F. Bloch, W. W. Hansen, and M. E. Packard, *Phys. Rev.*, *69*, 127 (1946); *70*, 474 (1946).
42. R. B. Williams, *Ann. N. Y. Acad. Sci.*, *70*, 890 (1958).
43. A. Einstein, *Phys. Z.*, *18*, 121 (1917).
44. E. M. Purcell, *Phys. Rev.*, *69*, 681 (1946).
45. N. Bloembergen, E. M. Purcell, and R. V. Pound, *Phys. Rev.*, *73*, 679 (1948).
46. E. M. Purcell, H. C. Torrey, and R. V. Pound, *Phys. Rev.*, *69*, 37 (1946).
47. F. Bloch, W. W. Hansen, and M. E. Packard, *Phys. Rev.*, *69*, 127 (1946).
48. G. V. D. Tiers, *J. Phys. Chem.*, *62*, 1151 (1958).
49. J. R. Zimmerman and M. R. Foster, *J. Phys. Chem.*, *61*, 282 (1957).
50. E. L. Hahn and D. E. Maxwell, *Phys. Rev.*, *84*, 1246 (1951).
51. H. S. Gutowsky, D. W. McCall, and C. P. Slichter, *Phys. Rev.*, *84*, 589 (1951).
52. N. F. Ramsey, *Phys. Rev.*, *91*, 303 (1953).
53. N. F. Ramsey and E. M. Purcell, *Phys. Rev.*, *85*, 143 (1952).
54. J. E. Wertz, *Chem. Revs.*, *55*, 829 (1955).
55. J. D. Roberts, *Nuclear Magnetic Resonance Applications to Organic Chemistry*, McGraw-Hill, New York, 1959.
56. A. Saika and H. S. Gutowsky, *J. Am. Chem. Soc.*, *78*, 4818 (1956).
57. C. M. Sharts and J. D. Roberts, *J. Am. Chem. Soc.*, *79*, 1008 (1957).
58. D. F. Evans, *Proc. Chem. Soc.*, *1958*, 115.
59. A. D. Cohen, N. Sheppard, and J. J. Turner, *Proc. Chem. Soc.*, *1958*, 118.
60. H. S. Gutowsky *et al.*, to be published.
61. M. Karplus and H. S. Gutowsky, 133rd Meeting, ACS, San Francisco, Calif., April, 1958.
62. M. Karplus, D. H. Anderson, T. C. Farrar, and H. S. Gutowsky, *J. Chem. Phys.*, *27*, 597 (1957).
63. H. M. McConnell, *J. Chem. Phys.*, *24*, 460 (1956).
64. A. A. Bothner-By, C. Naar-Colin, and B. L. Shapiro, *NMR Spectra and Structure Correlations*, Vol. II, January, 1958 (a privately circulated document).
65. G. V. D. Tiers, to be published.
66. J. A. Pople, W. G. Schneider, and H. J. Bernstein, *Can. J. Chem.*, *35*, 1060 (1957).
67. R. J. Abraham, J. A. Pople, and H. J. Bernstein, *Can. J. Chem.*, *36*, 1302 (1958).
68. D. Whitman, L. Onsager, M. Saunders, and H. Dubb, *J. Chem. Phys.*, *32*, 67 (1960).
69. C. Naar-Colin and A. A. Bothner-By, private communication.
70. H. Eyring, J. Walter, and G. E. Kimball, *Quantum Chemistry*, Wiley, New York, 1944, p. 126.

71. R. E. Glick and A. A. Bothner-By, *J. Chem. Phys.*, *25*, 362 (1956).
72. W. Anderson and H. M. McConnell, *J. Chem. Phys.*, *26*, 1496 (1957).
73. H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, *21*, 1688 (1953).
74. H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, *25*, 1228 (1956).
75. A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, *78*, 5126 (1956).
76. J. J. Drysdale and W. D. Phillips, *J. Am. Chem. Soc.*, *79*, 319 (1957).
77. C. E. Looney, W. D. Phillips, and E. L. Reilly, *J. Am. Chem. Soc.*, *79*, 6136 (1957).
78. W. D. Phillips, *Ann. N. Y. Acad. Sci.*, *70*, 817 (1958).
79. P. M. Nair and J. D. Roberts, *J. Am. Chem. Soc.*, *79*, 4565 (1957).
80. W. G. Schneider and L. W. Reeves, *Ann. N. Y. Acad. Sci.*, *70*, 858 (1958).
81. H. S. Jarrett, M. S. Sadler, and J. N. Shoolery, *J. Chem. Phys.*, *21*, 2092 (1953).
82. L. W. Reeves, *Can. J. Chem.*, *35*, 1351 (1957).
83. J. Musher and R. E. Richards, *Proc. Chem. Soc.*, *1958*, 230.
84. W. D. Kumler, J. N. Shoolery, and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, *80*, 2533 (1958).
85. W. G. Schneider, H. J. Bernstein, and J. A. Pople, *J. Am. Chem. Soc.*, *80*, 3497 (1958).
86. L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, *82*, 2184 (1960).
87. E. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glazier, *J. Am. Chem. Soc.*, *80*, 1204 (1958).
88. S. G. Smith and S. Winstein, *Tetrahedron*, *3*, 317 (1958).
89. T. A. Manuel and F. G. A. Stone, *Proc. Chem. Soc.*, *1959*, 90.
90. A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, *81*, 667 (1959).
91. J. E. H. Hancock and D. R. Scheuchenplug, *J. Am. Chem. Soc.*, *80*, 3621 (1958).
92. K. L. Rinehart, Jr., W. A. Nilsson, and H. A. Whaley, *J. Am. Chem. Soc.*, *80*, 503 (1958).
93. A. C. Cope, P. T. Moore, and W. R. Moore, *J. Am. Chem. Soc.*, *80*, 5506 (1958).
94. J. C. Sheehan, W. B. Lawson, and R. J. Gaul, *J. Am. Chem. Soc.*, *80*, 5536 (1958).
95. P. Yates and G. H. Stout, *J. Am. Chem. Soc.*, *80*, 1691 (1958).
96. D. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Linn, J. P. McPherson, and K. Folkers, *J. Am. Chem. Soc.*, *80*, 4752 (1958).
97. H. Conroy, P. R. Brook, M. K. Rout, and N. Silverman, *J. Am. Chem. Soc.*, *80*, 5178 (1958); H. Conroy, P. R. Brook, and Y. Amiel, *Tetrahedron Letters*, No. 11, 4 (1959).
98. E. J. Corey, H. J. Burke, and W. A. Remers, *J. Am. Chem. Soc.*, *77*, 4941 (1955).
99. W. von E. Doering, G. Laber, R. Vonderwahl, N. F. Chamberlain, and R. B. Williams, *J. Am. Chem. Soc.*, *78*, 5448 (1956).
100. C. J. Collins, W. T. Rainy, W. B. Smith, and I. A. Kaye, *J. Am. Chem. Soc.*, *81*, 460 (1959).
101. R. J. Gillespie, A. Grimison, J. H. Ridd, and R. F. M. White, *J. Chem. Soc.*, *1958*, 3228.

102. J. J. Drysdale, W. W. Gilbert, H. K. Sinclair, and W. H. Sharkey, *J. Am. Chem. Soc.*, *80*, 3672 (1958).
103. T. L. Jacobs and R. S. Bauer, *J. Am. Chem. Soc.*, *81*, 606 (1959).
104. B. E. Cross, J. F. Grove, J. MacMillan, T. P. C. Mulholland, and N. Sheppard, *Proc. Chem. Soc.*, *1958*, 221.
105. L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, *1958*, 196.
106. R. Morris, C. A. Vernon, and R. F. M. White, *Proc. Chem. Soc.*, *1958*, 303.
107. J. A. Elvidge, *J. Chem. Soc.*, *1959*, 474.
108. J. E. Nordlander and J. D. Roberts, *J. Am. Chem. Soc.*, *81*, 1769 (1959).
109. F. A. Cotton and J. R. Leton, *J. Am. Chem. Soc.*, *80*, 4823 (1958).
110. F. F. Caserio, Jr., S. H. Parker, R. Piccolini, and J. D. Roberts, *J. Am. Chem. Soc.*, *80*, 5507 (1958).
111. E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, *80*, 6686 (1958).
112. R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Am. Chem. Soc.*, *80*, 2237 (1958).
113. A. F. E. Sims and P. W. G. Smith, *Proc. Chem. Soc.*, *1958*, 282.
114. M. S. Barber, L. M. Jackman, and B. C. L. Weedon, *Proc. Chem. Soc.*, *1959*, 96.
115. E. E. van Tamelen, S. H. Levin, G. Brenner, J. Wolinsky, and P. E. Aldrich, *J. Am. Chem. Soc.*, *81*, 1666 (1959); *80*, 501 (1958).
116. H. Conroy and J. K. Chakrabarti, *Tetrahedron Letters*, No. 4, 6 (1959).
117. J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959.
118. L. M. Jackman, *Applications of Nuclear Magnetic Resonance in Organic Chemistry*, Pergamon Press, London, 1959.
119. M. Karplus, *J. Chem. Phys.*, *30*, 11 (1959); M. Karplus and D. H. Anderson, *J. Chem. Phys.*, *30*, 6 (1959).
120. H. Conroy, to be published.

HYDROGENATION-DEHYDROGENATION REACTIONS

By L. M. JACKMAN, *Imperial College of Science and Technology, London, England*

CONTENTS

I. Introduction 329
II. Homogeneous Hydrogen Transfer 330
A. Quinone Dehydrogenation 331
B. Dehydrogenation by Acceptors Other Than Quinones 345
C. Homogeneous Transfer Hydrogenation 348
III. Catalytic Hydrogen Transfer 349
A. Catalytic Transfer Hydrogenation 350
B. Catalytic Transfer Dehydrogenation 352
IV. Photochemical Hydrogen Transfer 355
V. Biochemical Hydrogen Transfer 356
VI. Experimental Procedures for the Preparation and Use of High Potential Quinones 359
References 363

I. Introduction

Hydrogenation-dehydrogenation reactions may be defined as processes in which pairs of hydrogen atoms are removed from a compound and added to another compound or element. The reduction process is then said to be *hydrogenation*, and its oxidation counterpart is termed *dehydrogenation*. In organic chemistry these reactions frequently involve the consumption or evolution of molecular hydrogen and are invariably carried out under the influence of solid phase catalysts. There is a vast literature concerning such processes which therefore lies outside the scope of the present chapter.*

* Although no attempt has been made to compile a bibliography in this area, mention should be made of the series *Advances in Catalysis*, Academic Press, Inc., New York, containing the following pertinent chapters: J. G. Tolpin, G. S. John, and E. Field, Vol. V, p. 266 (1953); E. Cremer, Vol. VII, p. 75 (1955); V. I. Komarewsky and J. R. Coley, Vol. VIII, p. 207 (1956); C. H. Johns and G. A. H. Elton, Vol. IX, p. 587 (1957); H. C. Rowlinson and R. J. Cvetanovic, Vol. IX, p. 243 (1957); A. A. Balandin, Vol. X, p. 96 (1958). Mention might also be made of the chapter on catalytic dehydrogenation by K. K. Kearby in P. H. Emmett, ed., *Catalysis*, Vol. III, Reinhold Publishing Corp., New York, 1955.

In addition to reactions involving molecular hydrogen, there is an important group of processes in which the pairs of hydrogen atoms are transferred from one molecular species to another and which can be symbolized by the following equation.

$$A + DH_2 \rightarrow AH_2 + D$$

In such systems, which have been termed hydrogen transfer systems, it is possible to recognize an acceptor molecule (A) and a donor molecule (DH_2) (1). Although in many instances hydrogen transfer reactions merely provide useful alternatives to catalytic hydrogenation and dehydrogenation, there are occasions where their use is attended by striking advantages. Hydrogen transfer therefore has its place among the tools of the organic chemist, and it is the purpose of this chapter to outline the uses which may be made of the method. In some cases the transfer systems involve inorganic donors (e.g., metal hydrides) or acceptors (e.g., sulfur and selenium dehydrogenation) and constitute well-known and well-reviewed methods. Accordingly, the scope of this chapter is further limited to include only those hydrogen transfer reactions in which both the donor and acceptor are organic molecules.

When a hydrogen transfer takes place, hydrogenation and dehydrogenation are of course occurring simultaneously. It is, however, convenient to classify these reactions according to the end in view. Thus, if the product of the hydrogen donor is desired, the reaction will be called dehydrogenation; conversely, a reaction in which the product of the acceptor is sought will be hydrogenation.

Organic hydrogen transfer reactions will be considered under the following headings: (*1*) homogeneous or thermal reactions, (*2*) heterogeneously catalyzed reactions, (*3*) photochemical transfers, and (*4*) biochemical processes. At the present state of our knowledge there is no obvious close relation among these various types, and the breakdown of the subject matter in this way is therefore arbitrary.

II. Homogeneous Hydrogen Transfer

The term homogeneous organic hydrogen transfer could include a number of important reactions which involve catalysis by inorganic derivatives, such as the Meerwein-Ponndorf reduction and the Oppenauer oxidation. These reactions have been the subjects of recent reviews (2–4), and accordingly the emphasis in this section is

directed toward those reactions which do not necessarily proceed through the intermediacy of some inorganic compound. The principal problem involved in developing reactions of this type is one of designing sufficiently powerful oxidizing and reducing agents. Quinones comprise the most powerful class of organic oxidizing agents, and they are finding increasing utility as dehydrogenating agents. Other acceptors have been of limited use. Hydrogenation by organic reductants has found little application, since it is difficult to obtain donors of sufficient activity and stability.

A. QUINONE DEHYDROGENATION

The use of a quinone for the dehydrogenation of hydroaromatic compounds was first reported by Clar and John (5) in 1930, although it had been observed earlier that 1,2-dihydrocarbazole was partially dehydrogenated by *p*-benzoquinone (6). Although the method has since been employed on a number of occasions, it has not been adopted to the extent it probably merits. This is doubtless due to the fact that it has not been generally realized that the method offers a number of advantages and that chloranil, the quinone most frequently used, is not one of the most effective quinones for the purpose.

1. Mechanism. As the most effective use of a reaction can only be made if its mechanism is understood, it is relevant at this stage to summarize briefly the main mechanistic features of the quinone-dehydrogenation reaction.

The mechanism has been established as a two-stage ionic process (7–11). The most compelling evidence for the ionic mechanism arises from the occurrence of a number of neighboring-group effects similar to those which often accompany unimolecular solvolysis (9–11). It is possible and even likely that the initial step in the overall reaction sequence is the formation of a charge transfer complex between donor and acceptor (12) analogous to that postulated in the Diels-Alder reaction (13). The various stages in the reaction between *p*-benzoquinone and 1,4-dihydrobenzene are illustrated in Figure 1.

Several conclusions concerning acceptor efficiency and donor reactivity may immediately be drawn. It is clear that electron-withdrawing substituents should increase the dehydrogenating power of quinones. Such changes in substitution similarly affect the oxidation-reduction potential of the quinone, and, in fact, linear free energy relationships between redox potential and reactivity in dehy-

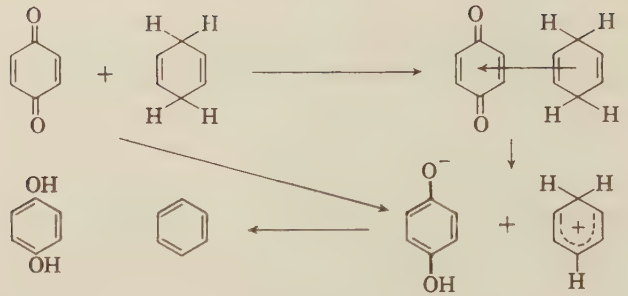


Figure 1

drogenation have been established (7,14) so that it is now known that quinones with high potentials will necessarily be the most powerful acceptors in dehydrogenation.

Similarly, it is to be expected that electron-donating substituents will increase the sensitivity of donors toward dehydrogenation. This has been confirmed experimentally for a series of 6- and 7-substituted 1,2-dihydronaphthalenes (12). The rates correlate with the Hammett σ, or better still σ^+ (15), values of the substituents, and the observation $\rho = -2.7$ is indicative of a fairly high sensitivity toward changes in substitution.

As the same type of intermediate is involved in quinone dehydrogenation and the unimolecular solvolysis of, say, alkyl halides, these reactions will have many characteristics in common. Indeed, a useful rule of thumb for assessing the ease and course of dehydrogenation of a donor is to imagine the potential hydride ion to be replaced by halogen and then to consider the reactivity of the resulting halide. Dehydrogenation is the counterpart of simple elimination (E_1), but just as elimination is but one of a number of reactions which can accompany unimolecular solvolysis, so is it found that with the quinone reaction there are interesting pathways other than dehydrogenation which may be taken. Some of the major advantages of quinones as oxidants are concerned with these alternative reactions, and illustrative examples are given below.

2. Suitable Quinones and Their Side Reactions. Most of the uses of quinone dehydrogenation reported in the literature employ chloranil (tetrachloro-1,4-benzoquinone) as an acceptor. This quinone has the merit of being reasonably stable and readily available, but it does not possess the reactivity exhibited by quinones which have

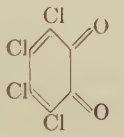
TABLE I
Relative Rate of Dehydrogenation of
1,2-Dihydronaphthalene at 100°

Quinone	$E°$	Relative rate
Chloranil	0.70	1
3,3′,5,5′-Tetrachloro-4,4′-diphenoquinone	ca. 1.0	1100
Tetrachloro-1,2-benzoquinone	0.87	4200
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	ca. 1.0	5500

appreciably higher redox potentials (16). The advantage in reactivity which attends the use of high potential quinones is well illustrated in Table I.

Among the high potential quinones at present available three—namely, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (I), tetrachloro-1,2-benzoquinone (II), and 3,3′,5,5′-tetrachloro-4,4′-diphenoquinone (III)—are probably the most useful. All are susceptible to various side reactions, but as will be shown below, the three quinones are to some extent complementary in this respect. Details of the preparations of these quinones are given in Section VI. It is probable that quinones with even higher potentials could be prepared. Cyano-substituted *o*-quinones would undoubtedly be most reactive. It should be noted that an *o*-quinone is, in general, more reactive than a *p*-quinone with the same potential, presumably because of strong hydrogen bonding in the transition state leading to the catecholate type mono-anion (7).

(I)

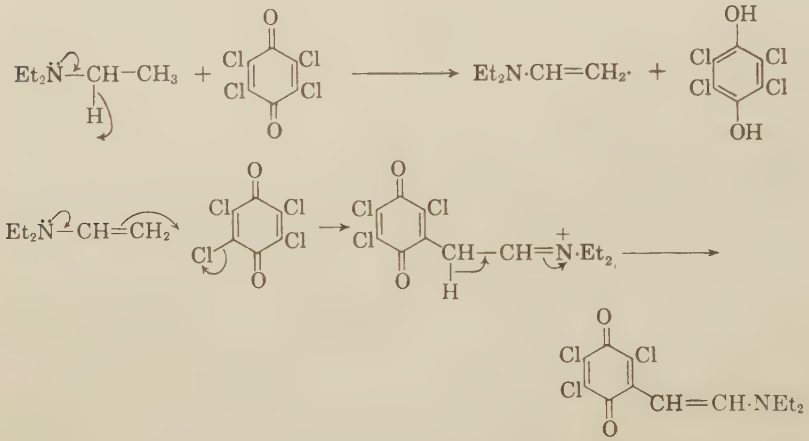


(II)

(III)

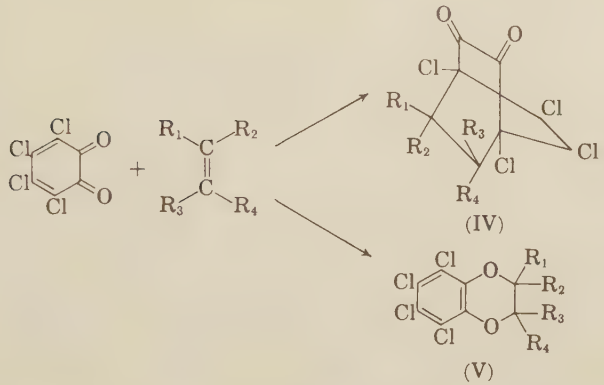
Before outlining the scope of quinone dehydrogenation, it is rather important to give a brief survey of the side reactions which may accompany and, in some systems, completely overshadow the dehydrogenation process. The most common side reactions are diene addition (Diels-Alder reaction), nucleophilic addition (in the case of unsubstituted quinones), and nucleophilic substitution (with halogenated quinones).

Chloranil is not a particularly powerful dienophile, but nevertheless it does undergo the Diels-Alder reaction (17,18). However, the only systems in which this type of side reaction has been shown to interfere with dehydrogenation are those in which polyacenes are produced (5,19). Replacement reactions are rather more serious and frequently arise when either the donor or its product is an amine. Thus, although chloranil can convert simple amines to enamines, the products isolated correspond to a subsequent attack by the enamine on the quinone (20).



2,3-Dichloro-5,6-dicyano-1,4-benzoquinone must be one of the most powerful dienophiles known, probably being comparable in reactivity with tetracyanoethylene (21). For example, it will form an adduct with anthracene in the cold. This reactivity can be a serious disadvantage, since adduct-forming reactions may compete successfully with dehydrogenation whenever the donor, product, or any of the intermediates contains a reactive diene system. It is probable that this quinone is also sensitive to replacement reactions, but there are no relevent data available. It is known that dicyanoquinones are sensitive to hydrolysis by moisture and that hydrocyanic acid is evolved in the reaction (22). For this reason it is essential to use the quinone under anhydrous conditions.

Tetrachloro-1,2-benzoquinone is itself a weak dienophile. It does, however, undergo two types of addition reactions with olefins which lead to the adducts IV or V. These adducts have been investigated by Horner and Merz (23). The formation of the type IV adduct is

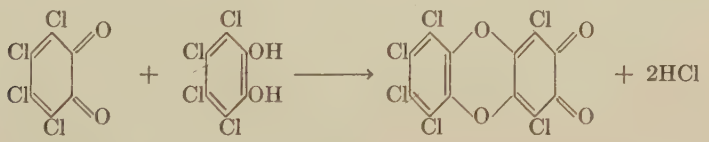


(IV)

(V)

energetically favored but is very susceptible to steric effects with the result that it is formed only from monosubstituted or *cis*-disubstituted olefins. In all other cases the dioxin (V) results. The formation of these adducts is, of course, readily recognized by the isolation of chlorine-containing products, and the two types are distinquished by their infrared spectra. Type IV adducts exhibit a carbonyl stretching band near 1760 cm.$^{-1}$, whereas the dioxin type (V) is characterized by a very intense band at 1420 cm.$^{-1}$ (10).

Tetrachloro-1,2-benzoquinone also undergoes a variety of replacement reactions, many of which have been studied by Jackson and his co-workers (24). The side reaction most commonly encountered in dehydrogenation reactions involves an interaction of the quinone with its hydroquinone leading to the formation of the new quinone (VI) and two molecules of hydrogen chloride. This reaction is relatively slow and is only significant in dehydrogenations which proceed with difficulty. However, the hydrogen chloride which accompanies the formation of VI can sometimes be annoying in that it may lead to acid-catalyzed reactions of the donor.



(VI)

Jackson reports that the quinone reacts readily with aniline, alcohols, benzaldehyde, and acetone. Many of the structures assigned

to the products are clearly incorrect (25), and the chemistry of this quinone requires reinvestigation. It is apparent that the presence in the donor of any potential nucleophile can lead to side reactions, but frequently the substitution reactions are too slow to compete with the dehydrogenation process.

3,3′,5,5′-Tetrachloro-4,4′-diphenoquinone offers the great advantage of not undergoing addition reactions (26), but it does appear to be rather sensitive to hydrolysis and other replacement reactions (27).

Although halogen replacement reactions occur quite readily, halogen substitution in the quinones is still a desirable feature since it not only increases the acceptor reactivity but also confers greater thermal stability to the quinone. For instance, 1,2-benzoquinone is notoriously unstable, whereas its tetrachloro derivative is thermally stable up to its melting point (130°). Furthermore, the absence of halogen substituents does not remove reactivity toward nucleophiles, since unsubstituted quinones may undergo nucleophilic addition with the formation of substituted hydroquinones.

Perhaps the most stable quinones, which still have sufficient reactivity to be useful reagents for dehydrogenation, are phenanthraquinone and its derivatives. Phenanthraquinone cannot undergo diene addition reactions, nor is it capable of reacting with nonionic nucleophiles. It is known to form a type V adduct, but only in a photocatalyzed reaction (28). 2,7-Dinitrophenanthraquinone is more reactive than the parent quinone but has the disadvantage of being rather insoluble in most suitable solvents.

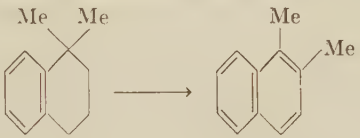
3. Scope and Limitations. In spite of the depressing number of side reactions outlined above, it is possible by a judicious choice of reagent to dehydrogenate a great variety of structures by quinones. These reactions can be conducted at moderate temperatures and do not require special apparatus or techniques.

One of the major uses of chloranil has been for the dehydrogenation of carbocyclic compounds for which the method is particularly simple and convenient. High potential quinones can also be used and often result in improved yields. *p*-Benzoquinones should be avoided for the dehydrogenation of 1,3-cyclohexadienes or of the higher hydropolyacenes (Section II-A-2). It must be stressed that even the high potential quinones are incapable of dehydrogenating completely saturated carbocycles (29). Some degree of activation is required. A double bond or benzene ring is sufficient. Thus, decalin is inert to

quinone dehydrogenation, whereas octalins and tetralin are converted to naphthalene.

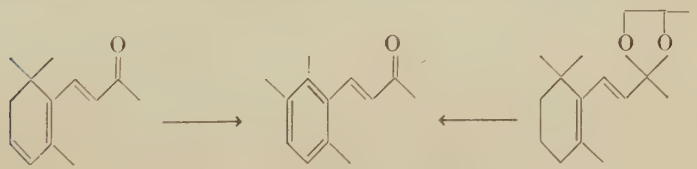
Ring size has a profound effect on the ease of dehydrogenation, and it is found that indane and tetralin react much more readily than benzocycloheptene (30). This is in accord with the mechanistic theory (Section II-A-1), as a similar reactivity sequence has been established for the solvolyses of the 1-chloro derivatives of these three hydrocarbons (31). Similarly, aliphatic side chains are inert under conditions where the five- and six-membered rings are rapidly dehydrogenated. As a consequence, quinones may be used specifically to aromatize structures without affecting alkyl side chains.

The principal advantage of quinone dehydrogenation in the carbocyclic series is that it provides a unique method of aromatizing rings containing quaternary carbon atoms without the loss of carbon atoms. For example, 1,1-dimethyltetralin (VII) is converted to



(VII)

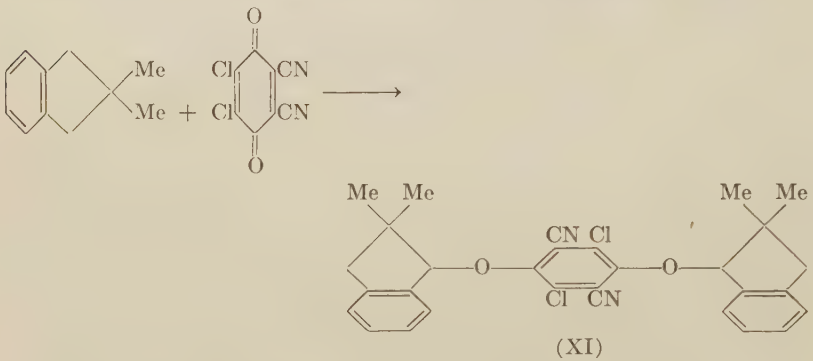
1,2-dimethylnaphthalene. The majority of dehydrogenation methods when applied to "blocked" systems effect elimination of the blocking group (32). The ability of quinones to cause migration is, of course, completely consistent with the ionic mechanism. Furthermore, the unimolecular solvolysis analogy (Section II-A-1) points out that the presence of a "blocking" group will in no way hinder dehydrogenation and, in suitable circumstances, may even assist the process (33). A number of examples of di- and tetrahydronaphthalenes which undergo quinone dehydrogenation with rearrangement are available and include the migrations of methyl, ethyl, isopropyl, and phenyl groups (10). The method has been successfully used for the preparation of 4-(3-pseudocumyl)but-3-en-2-one (IX) from dehydro-β-ionone (VIII)



(VIII) (IX) (X)

or, less effectively, from β-ionone propylene ketal (X) (10), an intermediate in the synthesis of a biologically active pseudocumyl analog of vitamin A acid (34). Angular methyl groups in simple systems such as 9-methyloctalin have been shown to migrate (10). However, the method is not satisfactory for the complete aromatization of steroids and other polycyclic systems. It seems that dehydrogenation of such systems is sterically inhibited at various points (probably ring junctions), and the partially dehydrogenated compounds have the opportunity to undergo side reactions. The extension to polycyclic systems has not been thoroughly investigated, and there are doubtless a number of useful partial dehydrogenations which could be effected by quinones.

It is interesting to note that an attempt to induce a rearrangement in 2,2-dimethylindane resulted in a substitution reaction, the major product being the bisindanyl ether of the hydroquinone (XI) (10).



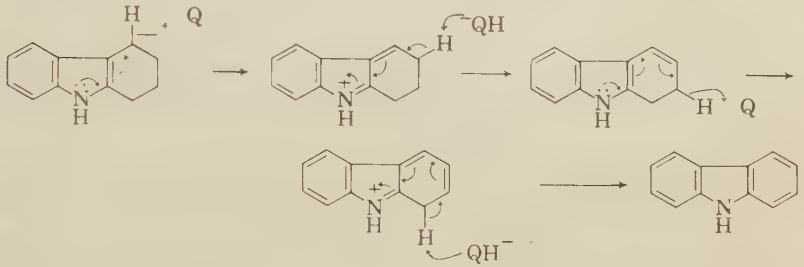
(XI)

Although acyclic hydrocarbons react far less readily than similarly activated carbocycles, quinones can be employed for the introduction of ethylenic double bonds. Thus, dibenzyl yields *trans*-stilbene with high potential quinones (16), and $Ph_2C{=}CHCH_2CH_2CH{=}CPh_2$ is converted to the hexatriene by chloranil. Chloranil has also been used for the dehydrogenation stage in the degradation of C^{14}-labeled 1,1,2-triphenylethane.

$$Ph_2\overset{*}{C}HCH_2Ph \rightarrow Ph_2\overset{*}{C}{=}CHPh$$

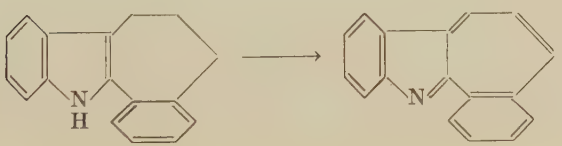
The appearance of 9% activity at carbon-2 was attributed to an isotopic impurity in the ethane, but it is conceivable that part of this activity arises via a hydride or a phenyl migration (35).

Quinones are particularly effective for the dehydrogenation of heterocyclic compounds. The lone pairs of electrons of the hetero atoms can provide considerable driving force for hydride ion abstraction, and ammonium, oxonium, and sulfonium cations are much more attractive intermediates than the carbonium ions derived from equivalent carbocyclic systems. This is well illustrated by the facile dehydrogenation of tetrahydrocarbazole by chloranil.



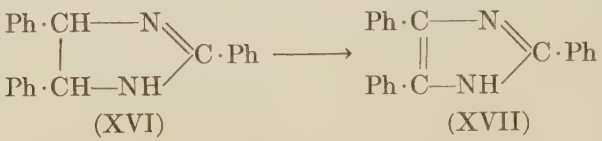
Indeed, chloranil provides the best method of dehydrogenating hydrocarbazoles. Barclay and Campbell have recorded the dehydrogenation of some 25 di-, tetra-, and hexahydrocarbazoles in yields ranging from 75 to 90% (36). Similarly, Buu-Hoï, Hoán, and Khôi have found the method useful for the dehydrogenation of a number of 3,4-dihydrodibenzcarbazoles (37). One particularly interesting example provided by Treibs and his co-workers is the conversion in 20–25% yields by chloranil of heptindole (XII) and the benzoheptindole (XIII) to the corresponding aza-azulenes (XIV and XV) (38). The nucleophilic character of the nitrogen atom is largely suppressed in indoles and carbazoles, and there is little chance of quaternization reactions with halogenated quinones. This does not apply to the products XIV and XV, and it is possible that the lower yields in which they are formed are a result of replacement reactions.

(XII) (XIV)



(XIII) (XV)

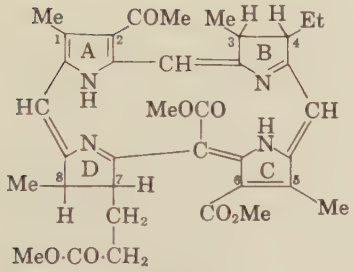
The dihydro derivatives of pyridine, quinoline, isoquinoline, acridine, and phenanthridine can all be dehydrogenated by quinones, and in most cases the reactions are very rapid (39,40). *N*-Methyl derivatives give the corresponding quaternary ammonium hydroquinolates. Attempts to dehydrogenate more highly reduced derivatives with halogenoquinones are not very successful, presumably because replacement reactions compete more favorably with the slower dehydrogenation process. This difficulty may be overcome by the use of phenanthraquinone or its derivatives. Thus, amarine (XVI) gives only brightly colored salts with benzoquinone, chloranil, and tetrachloro-1,2-benzoquinone, whereas it is converted smoothly to lophine (XVII) by phenanthraquinone (41).



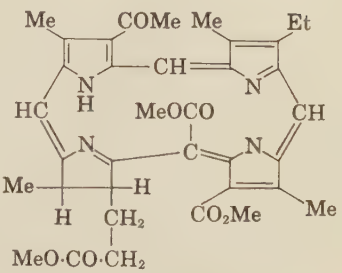
(XVI) (XVII)

The dehydrogenation of 1,2,3,4,-tetrahydroisoquinoline provides an example of the remarkable selectivity obtainable by the quinone method (40). So great is the driving force associated with the lone pair of electrons of the nitrogen atom that the rate of conversion of the tetrahydro compound to 3,4-dihydroisoquinoline is much greater than that of the subsequent aromatization step. As a consequence, it is possible to use phenanthraquinone or 2,7-dinitrophenanthraquinone to convert tetrahydroisoquinoline into 3,4-dihydroisoquinoline in high yield. Under more vigorous conditions, isoquinoline is formed. Although this is an isolated example, it is probable that the reaction will prove to be general and of some utility in isoquinoline chemistry.

Hydroporphins and the related tetraazaporphins can be smoothly dehydrogenated by high potential quinones, and the method provides an elegant means of establishing the hydrogenation level of both synthetic (42,43) and naturally occurring derivatives (44). The proof that bacteriochlorophyll possesses a tetrahydroporphin nucleus rests on the quantitative conversion, by one molecular equivalent of dichlorodicyanobenzoquinone at room temperature, of bacteriochlorin e_6 trimethyl ester (XVIII) to the corresponding chlorin (XIX). It is noteworthy that ring B alone suffers dehydrogenation, indicating a



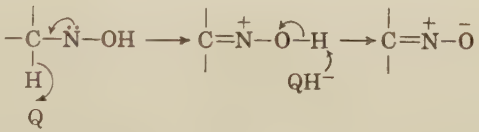
(XVIII)



(XIX)

rather serious distortion of ring D by the mesocarbomethoxy group. Thus, even at carbon 8 there is difficulty in forming a planar carbonium ion.

Acyclic amines are obviously capable of dehydrogenation to azomethines, but as mentioned above (Section II-A-2), they can then be involved in replacement reactions. It would be of interest to test phenanthraquinone in this connection as it cannot undergo replacement reactions. Closely related to the dehydrogenation of amines is the conversion of hydroxylamines to imine *N*-oxides which, as Rogers has shown, can be accomplished by benzoquinone (45).



The extension of quinone dehydrogenation to the preparation of furans has received little attention. Most probably, partial unsaturation or suitable substitution is necessary for reaction. It is reported that 2,5-dihydro-3-phenylfuran gives only 10% of the furan on treatment with chloranil (46) and it is possible that a Diels-Alder reaction between the quinone and the furan is responsible for the low yield. If this is the case, *o*-quinones and *p,p'*-diphenoquinones might well give better results. Flavanones can also be dehydrogenated to flavones (47), although it is not known whether 4-chromanone itself can be converted to chromone.

Attempts to convert 2,4-cycloheptadienone to tropone by dehydrogenation with either dichlorodicyanobenzoquinone or chloranil gave only low yields of the desired product (48). It has been pointed out that this donor is unfavorably activated for hydride ion abstraction. Nevertheless, it is conceivable that the reaction failed because of a

diene addition reaction, and it is possible that the use of tetrachlorodiphenoquinone might have proved successful.

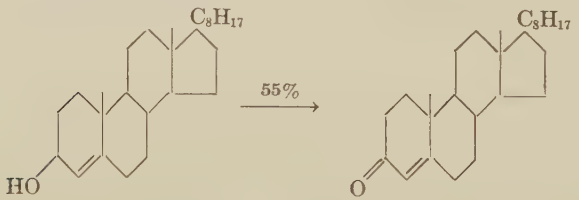
As with the furans, little is known about the utility of quinone dehydrogenation in thiophene chemistry. An attempt to dehydrogenate 3,4-dihydroxythiolane with chloranil was unsuccessful (49). However, dihydrothiophenes are readily dehydrogenated by chloranil, and the excellent yields observed suggest that this is the best method at present available (50). The thiophene nucleus is apparently stable to chloranil, for Buu Hoï and his co-workers have successfully aromatized several thiophenobenzodihydrocarbazoles with chloranil (51), and the same reagent has been used for the conversion of 2-(1-cyclohexenyl)thiophene to 2-phenylthiophene in high yield (52). If this is general, the method will be most useful in the field of polycyclic thiaheterocycles, since catalytic procedures are sometimes ruled out by the catalyst-poisoning properties of such donors.

Unless photocatalyzed, saturated primary and secondary alcohols do not undergo hydrogen transfer with quinones. In contrast, allylic, propargylic, and benzylic alcohols have been shown to be oxidized to the corresponding aldehydes or ketones by both chloranil (54) and tetrachloro-1,2-benzoquinone (53). Some examples are given below.

$$MeCH{=}CHCH{=}CHCH_2OH \xrightarrow{40\%} MeCH{=}CHCH{=}CHCHO$$

$$PhCH_2OH \xrightarrow{40\%} PhCHO$$

$$PhC{\equiv}CCH(OH)CH{=}CHPh \xrightarrow{91\%} PhC{\equiv}CCOCH{=}CHPh$$

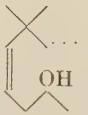


The reaction gives reasonable yields, and it may well prove to be a valuable alternative to manganese dioxide oxidation as, unlike the latter, it is a homogeneous process and therefore reproducible. Warren and Weedon have used chloranil oxidation for diagnostic purposes in the carotenoid field (54). They have shown that the hexaenediol (XXa) and tetraols (XXb and XXc) all undergo allylic

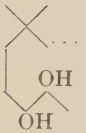
oxidation, but that the presence of a γ-hydroxyl substituent, as in XXd, inhibited the formation of diketone. Since the polyols derived from capsanthin and capsorubin could be oxidized to diketones, it was inferred that neither of these natural carotenoids contained hydroxyl groups in γ-positions.

(XX)

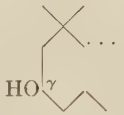
(XXa) R = CMe_3 (XXb) R =



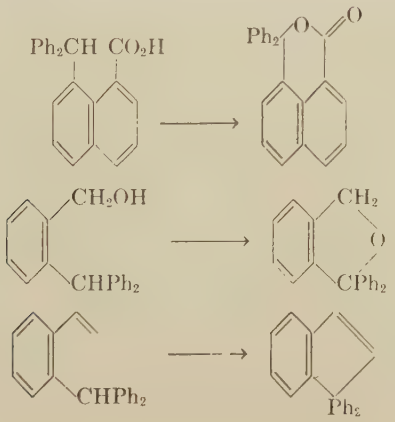
(XXc) R =



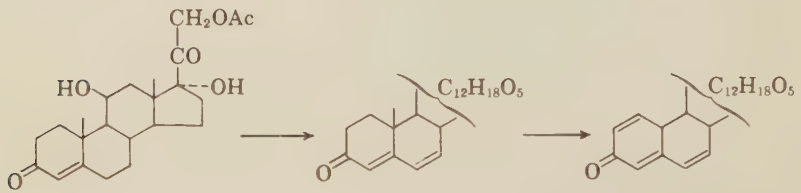
(XXd) R =



There are several examples of cyclodehydrogenation employing high potential quinones. Such reactions are closely related to cyclizations which, with suitable structures, can accompany unimolecular solvolysis. Lactones and cyclic ethers have been prepared in this way (11), and there is one example of the formation of a purely carbocyclic ring (55)

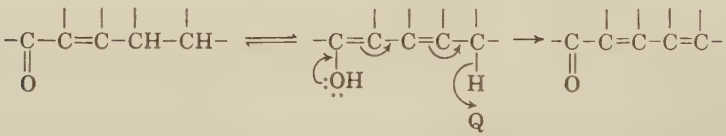


An interesting and potentially useful variant of quinone hydrogen transfer is the selective dehydrogenation of readily enolizable ketones which has been investigated by Agnello and Laubach (56). Chloranil in boiling xylene converts hydrocortisone acetate (XXI) into its Δ^6-dehydro derivative (XXII). More vigorous conditions afford Δ^6-dehydroprednisolone acetate (XXIII) which could also be ob-



(XXI) (XXII) (XXIII)

tained directly from prednisolone acetate. It has been suggested that this reaction can also be accounted for by a hydride ion abstraction mechanism (57).



It is unlikely that the scope of quinone dehydrogenation has been fully established. Apart from the synthesis of more active quinones, there are a number of ways in which the utility of the reaction might possibly be extended. Of these, the dehydrogenation of preformed anions is particularly attractive. It is known that ketones can accept hydride ions from primary and secondary alkoxide ions (58), and it is likely that suitable quinones would be more effective acceptors. For this purpose it would be necessary to use a quinone which is incapable of undergoing substitution or addition reactions with alkoxide ions.

Phenanthraquinone might be suitable provided a benzilic acid rearrangement did not interfere. In the same way it might be

feasible to extend Agnello's reaction to a stepwise introduction of double bonds into a ketone by working with preformed enolate ions.

As a final variant there is the attractive possiblity of achieving a decarboxylative dehydrogenation by the action of quinones on carboxylate ions.

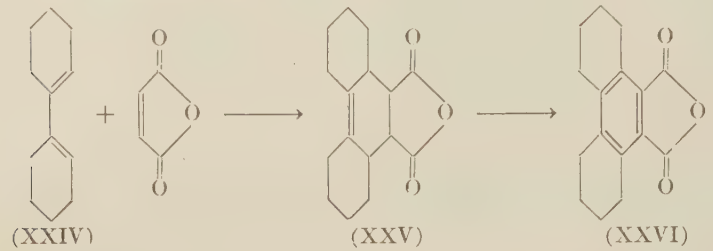
This reaction has a counterpart in the base-catalyzed elimination of the elements of carbon dioxide and hydrogen bromide from β-bromo acids. To effect the reaction it would presumably be desirable to use a salt, such as the tetraamyl ammonium salt, which would be reasonably soluble in organic solvents. Alternatively, it should be possible to synthesize a water-soluble quinone, conceivably a quaternary ammonium base.

B. DEHYDROGENATION BY ACCEPTORS OTHER THAN QUINONES

Quinones are by no means unique in their ability to accept hydrogen from other organic molecules. They are, however, the most powerful class of organic acceptors at present available. Occasionally other acceptors have found uses in preparative chemistry. Of these, nitrobenzene is the most important because it is readily available and can be used as a solvent as well as a reactant. For this reason nitrobenzene has been employed in several reactions for dehydrogenating initial and unstable products and two such processes are now discussed.

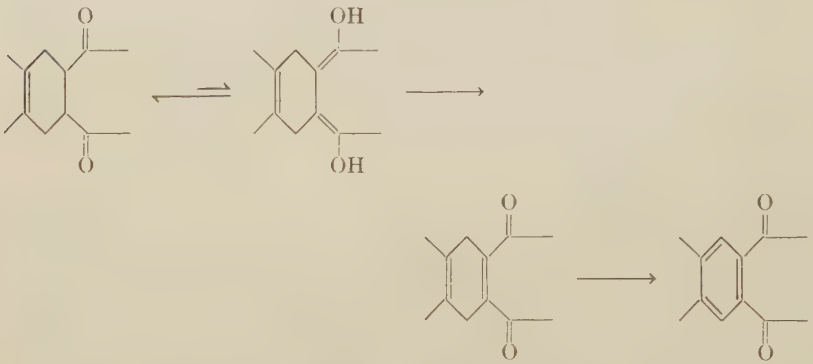
Certain hydroaromatic compounds prepared by the Diels-Alder reaction can be dehydrogenated by nitrobenzene (58–63), and if the addition reaction is carried out in nitrobenzene as a solvent, the fully aromatized product is often formed directly in enhanced yields. For example, 1,1′-dicyclohexenyl (XXIV) reacts with maleic anhydride in nitrobenzene to give the partially aromatized perhydrophenan-

threne (XXVI). If the addition is carried out in a nonacceptor solvent, the intermediate adduct XXV is isolated.

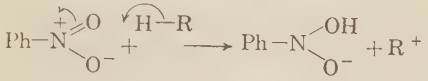


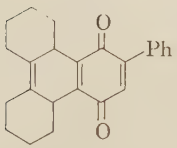
(XXIV) (XXV) (XXVI)

Bergmann has shown that a necessary structural requirement for the dehydrogenation is the presence of *two* vicinal enolizable groups. Thus, initial hydrogen transfer is from the dienol and leads to a 1,4-dihydrobenzene derivative which is itself an active donor and usually suffers further dehydrogenation.



The dienol formed from a quinone adduct is of course a hydroquinone, whereas that derived from a maleic anhydride adduct is a similarly constituted structure. Both types will very readily undergo transfer reactions. However, the subsequent dehydrogenation of the 1,4-dihydrobenzene does not always occur. Thus, the reaction between 1,1′-dicyclohexenyl and 2-phenyl-1,4-benzoquinone in nitrobenzene yields the quinone (XXVII). This is probably a result of the deactivating influence of the two carbonyl groups which in the anhydrides is largely neutralized by the ether oxygen atom. Such deactivation would be in agreement with a plausible mechanism involving hydride ion abstraction by nitrobenzene.

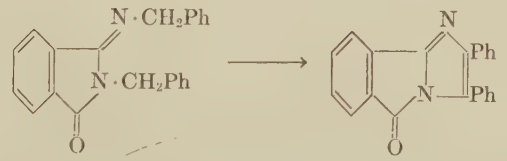




(XXVII)

Nitrobenzene and other aromatic nitro compounds are also effective for the dehydrogenation of certain hydroaromatic heterocycles (64), such as 1,2-dihydroquinoline, and for this reason they are often used in the Skraup reaction (65). 1,2-Dihydroquinoline is apparently the initial product of the Skraup reaction, and, in order to obtain good yields of the desired quinoline, it is necessary to provide for the immediate oxidation of the intermediate. The nitro compound employed usually has to correspond to the particular amine undergoing reaction, although picric acid apparently may be used more generally (66).

Benzylamine is capable of acting as a hydrogen acceptor, although its more usual role is that of a donor (Section II-A-3). Elvidge and Chapman have found that benzylamine at 230° effects cyclodehydrogenation followed by dehydrogenation of the imide (XXVIII), and that amarine (XVI) is converted to lophine (XVII) under the same conditions (67). Toluene and ammonia are the products from the acceptor.



(XXVIII)

Other acceptors which have been used in hydrogen transfer reactions include methyleneimine and its salts (68–71), Schiffs bases (68, 69), formylamines (69), methylenebisamines (69, 72), formamidines (69), isatin (73), alloxan (73), disulfides (74), and *N*-sulfinylani-

line (75). Carbonium ions have also been shown to possess acceptor properties (76,77).

C. HOMOGENEOUS TRANSFER HYDROGENATION

In the preceding section hydrogen transfer was discussed from the standpoint of dehydrogenation with emphasis on the reactivity of the acceptor molecule. It was noted, however, that certain donors, particularly some hydroaromatic heterocycles, were very readily dehydrogenated, and the possibility exists that such donors might find use as hydrogenating agents. The scope of some of the more powerful donors has been investigated by Braude, Hannah, and Linstead (39), and the more important results obtained with the Hantzsch ester diethyl 1,4-dihydro-2,6-lutidine-3,5-dicarboxylate are summarized in Table II. Although other donors, such as 1,2-dihydroquinoline, are somewhat more active than the Hantzsch ester, their intrinsic instability renders them less effective in practice.

TABLE II
Transfer Hydrogenation with the Hantzsch Ester (39)

Acceptor	Product	Temp., °C.	Time, hr.	Yield, %
Chloranil	Tetrachlorohydroquinone	25	0.25	97
Maleic acid	Succinic acid	66	72	72
Maleic anhydride	Succinic anhydride	101	0.5	91
Diethyl maleate	Diethyl succinate	172	20	76
Diethyl fumarate	Diethyl succinate	172	20	70
Dimethylmaleic anhydride	Dimethylsuccinic anhydride[a]	172	90	53
Δ^1-Tetrahydrophthalic anhydride	*cis*-Δ^1-Hexahydrophthalic anhydride	172	85	70
Benzalacetophenone	Benzylacetophenone	172	85	80
Benzil	Benzoin	172	24	23
Benzalaniline	Benzylaniline	156	24	45
Azobenzene	Hydrazobenzene	156	24	30

[a] Meso, 11%; racemic, 89%.

Compounds which did not undergo transfer hydrogenation with the Hantzsch ester included cinnamic acid, diphenylacetylene, stilbene, *p*-cyanostilbene, benzophenone, mesityl oxide, and anthracene. If it is assumed that these reactions are ionic in character, then it

would appear that transfer requires of the acceptor a sensitivity toward nucleophilic addition of the same order as is required for the Michael addition. Thus, only activated double bonds can be hydrogenated by this method.

An interesting class of transfer involves hydroaromatic and aromatic heterocyclic pairs. The Hantzsch ester has been shown to convert quinoline and isoquinoline to their tetrahydro derivatives, and acridine and phenanthridine to their dihydro derivatives. Similarly, 1,2-dihydroquinoline reduces acridine to dihydroacridine. It is possible that the reaction could be used to evaluate the ease of reduction of this type of heterocycle, and the results should correlate with theoretically calculable quantities.

The results contained in Table II show that even for favorable systems quite vigorous conditions are required for transfer. Therefore, homogeneous hydrogen transfer is not a particularly attractive preparative method. Furthermore, the chances of developing more effective organic donors seem remote, since any increase in donor activity must inevitably be attended by increased instability. However, because of their close analogy to biological hydrogenase systems, transfer hydrogenations of the type discussed here may well assume considerable importance in the near future.

III. Catalytic Hydrogen Transfer

Homogeneous hydrogen transfer as a method of hydrogenation or of dehydrogenation is limited largely by the availability of donors and acceptors of sufficient activity to effect reaction at reasonable rates and temperatures. The limitation is therefore kinetic, rather than thermodynamic, in origin. For this reason metal catalysts enable donors and acceptors to be used which under homogeneous conditions would react infinitely slowly at temperatures which lie within the convenient range available to the organic chemist. A simple illustration is provided by the fact that, up to 600°, cyclohexene is perfectly stable and shows no tendency to disproportionate (78). In the presence of palladium black, disproportionation occurs rapidly at room temperature as evidence of the fact that, thermodynamically, cyclohexene can act as both an acceptor and donor.

The use of a catalyst makes it possible to employ readily available reagents. At the same time, the obvious disadvantages of metal catalysts now arise. The reactions are no longer necessarily repro-

ducible, and reactants must be of high purity. Nor is there available a simple theory of reaction mechanism which can serve as a guide for the design of experiments. It is now necessary to draw on experience or to proceed by trial and error, for many of the peculiarities of specificity which have been noted in catalyzed hydrogen transfer could certainly not have been predicted *a priori*.

A. CATALYTIC TRANSFER HYDROGENATION

In accordance with the present terms of reference, the source of hydrogen must be an organic molecule. The ideal donor must be readily available as well as reactive, and the final choice is to some extent governed by the catalyst employed.

Without doubt the preferred catalyst is palladium, either as palladium black or as palladized charcoal. Raney nickel and other nickel catalysts have also been used, usually with cyclohexanol as a donor (79–83), although there is often doubt as to whether reduction is effected by transfer or by direct hydrogenation with adsorbed hydrogen. Transfer hydrogenation with nickel catalysts usually requires long periods of heating at elevated temperatures and the yields are variable. In contrast, palladium-catalyzed transfers occur much more readily (often at room temperature) and usually give excellent yields (84–87) (Table III). With palladium as a catalyst, the choice of donor usually falls on cyclohexene. It has been shown that cyclohexene is comparable or better than most of the likely donors (85, 86) and has the advantage that it can often be used as a solvent for the reaction.

Palladium and cyclohexene can be used for the transfer hydrogenation of carbon–carbon double and triple bonds. Aromatic azomethines and azo compounds are also reduced, and the products obtained are those of hydrogenolysis. Halogen compounds suffer hydrogenolysis. Benzoyl chloride gives a low yield of benzaldehyde, but as this result is based on only one experiment it is possible that variation of conditions might well lead to a useful alternative to the Rosenmund reduction. Carbonyl and nitrile groups are not reduced, so that the method offers the same degree of selectivity as direct hydrogenation over the same catalyst. One notable exception is the failure of maleic anhydride to undergo transfer hydrogenation (84). It appears that maleic anhydride must be adsorbed on the catalyst

to the exclusion of the cyclohexene, for it inhibits both the disproportionation of the latter and transfer reactions with other acceptors.

The reduction of nitro groups by transfer hydrogenation with palladium and cyclohexene offers some definite advantages over direct hydrogenation and other conventional methods. Braude, Linstead, and Wooldridge have examined the reaction of 33 mononitro compounds and record excellent yields of amines in most cases. The three nitrobenzaldehydes resisted transfer hydrogenation. This is consistent with their behavior on direct hydrogenation over palladium. The three nitroanilines and *p*-bromoaniline also failed to undergo transfer hydrogenation, although these compounds are readily

TABLE III
Transfer Hydrogenation with Cyclohexene and Palladium (84,87)

Acceptor	Product	Yield, %
Allylbenzene	Propylbenzene	85
Propenylbenzene	Propylbenzene	85
Indene	Indane	95
trans-Stilbene	Dibenzyl	100
Tolane	Dibenzyl	100
Acenaphthylene	Acenaphthene	100
1,1-Diphenylethylene	1,1-Diphenylethane	85
But-3-enoic acid	Butyric acid	90
Crotonic acid	Butyric acid	89
Oleic acid	Stearic acid	40
Sorbic acid	Hexanoic acid	90
Cinnamic acid	β-Phenylpropionic acid	90
Maleic acid	Succinic acid	100
Muconic acid	Adipic acid	80
Benzylideneaniline	Aniline	44
Azobenzene	Aniline	97
Benzyl chloride	Toluene	50
Cinnamyl chloride	Propylbenzene	50
Benzoyl chloride	Benzaldehyde	10

hydrogenated by molecular hydrogen. Apparently certain groups, such as the $—NH_2$ group, can inhibit transfer. This observation, together with the fact that nitroanilines do not inhibit the disproportionation of cyclohexene (i.e., they are not catalyst poisons), suggests the requirement of a specific mutual orientation of donor and acceptor on the catalyst surface. The corresponding *N*,*N*-dialkyl

and N-acyl derivatives behave normally. The ability of free amino groups to inhibit the hydrogenation of a nitro group in the same molecule has a useful preparative aspect, for, as a consequence, it is sometimes possible to effect partial hydrogenation of polynitro compounds to the corresponding monoamines. Some examples are given in Table IV. The data in the table indicate that the presence of a free amine group does not always inhibit further reduction, and there appears to be no simple rule governing selectivity.

TABLE IV
Transfer Hydrogenation of Polynitro Compounds

Acceptor	Product	Yield, %
o-Dinitrobenzene	None	—
m-Dinitrobenzene	*m*-Nitroaniline	80
p-Dinitrobenzene	None	—
2,4-Dinitrotoluene	2,4-Diaminotoluene	75
1-*tert*-Butyl-2,4-dinitrobenzene	2,4-Diamino-1-*tert*-butylbenzene	95
1,8-Dinitronaphthalene	1,8-Diaminonaphthalene	97
2,4-Dinitrophenol	2,4-Diaminophenol	65
3,5-Dinitrobenzoic acid	3-Amino-5-nitrobenzoic acid	60
1,3,5-Trinitrobenzene	3,5-Dinitroaniline	9
Picric acid	Picramic acid	28

There are probably many other examples of selective reduction by transfer hydrogenation to be found. Unfortunately, as well illustrated by the preceding examples, there is no simple theory of mechanism which can be used for making predictions about untried systems. Thus at present transfer hydrogenation is generally merely an alternative to direct hydrogenation. As such it has the merit of requiring no specialized apparatus but the disadvantage that the course of reaction cannot be followed by gas uptake as in the direct method.

B. CATALYTIC TRANSFER DEHYDROGENATION

Like its hydrogenation counterpart, catalytic transfer dehydrogenation has found only occasional use as a preparative or degradative method. Yet the transfer reaction does not always follow the same course as the well established methods of dehydrogenation,

and for this reason it should be tried when other approaches have failed.

A number of catalysts, including platinum, palladium, and nickel, have been tried, and Adkins and his co-workers have made an extensive survey of the transfer dehydrogenation of polycyclic and heterocyclic compounds over these three catalysts with benzene as an acceptor (88–93). The reactions require elevated temperatures—usually exceeding 300° –and have therefore to be carried out in high pressure autoclaves. Reactions carried out in the presence of nickel catalysts are remarkably sensitive to the purity of the benzene and in the way least expected. Sulfur-free benzene is quite unsatisfactory as an acceptor. The addition of thiophene, or better still diphenyl sulfide, promotes the dehydrogenation. Tetramethyltin and carbon tetrachloride also exhibit promoter properties. Sulfur compounds do not increase the ease of transfer dehydrogenation over platinum or palladium. At the same time there is no evidence of the catalyst poisoning with which they are associated in catalytic hydrogenation.

Of the various catalysts examined by Adkins, nickel on kieselguhr is the most interesting, for it was found that transfer dehydrogenation of carbocyclic systems containing quaternary carbon atoms sometimes proceeded with migration of the blocking substitutent, whereas the other catalysts caused elimination of the group. It is interesting to contrast these reactions with quinone dehydrogenation (Section II-A-3) which also effects migration (see Table V). The nickel-catalyzed transfer is seen to compare very unfavorably with the quinone dehydrogenation when applied to systems to which the latter method is also applicable. However, the catalyzed process is probably the only method available for aromatizing a completely saturated

TABLE V

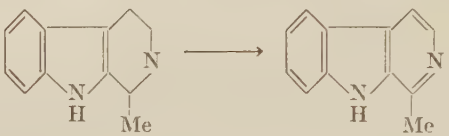
Dehydrogenation of 1,1-Dimethyl- and 1-Methyl-1-phenyltetralins

Method	Temp., °C.	Yield of rearranged product, %	
		1,1-Me_2	1-Me-1-Ph
Dichlorodicyanoquinone	80	77	—
Platinum-benzene	350	None	—
Reduced nickel chromite–benzene	370	None	—
Nickel on kieselguhr-benzene	350	35	None

carbocycle with migration of a blocking substituent. Unfortunately, the extent to which such reactions are successful is unknown.

Raney nickel is also active as a catalyst for transfer dehydrogenation, particularly for the oxidation of secondary alcohols (80). The preferred acceptor appears to be cyclohexanone, and this catalyst-acceptor combination has found use as a method of oxidizing 3-α- and 3-β-hydroxysteroids to the 3-keto compounds (80,94,95). The oxidation of glucose to glucuronic acid (81) and the dehydrogenation of tetrahydrocarbazole (96) have also been reported.

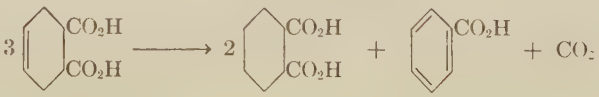
There is some evidence that palladium with suitable acceptors can bring about dehydrogenation at temperatures considerably lower than those employed by Adkins. Several acceptors have been tried by Akabori and his collaborators (97,98) who subsequently used maleic acid and palladium for the dehydrogenation of tetrahydro-



(XXIX)

harmane (XXIX) (99). The same combination successfully converts 1,2,3,4,-tetrahydro-4-oxoquinaldine to 4-oxyquinaldine (100).

Recent observations (86) made by Braude, Linstead, and Whiting concerning decarboxylation, which can accompany the mild transfer dehydrogenation of certain carboxylic acids, may lead to interesting syntheses of some types of aromatic compounds. It was noted that the palladium-catalyzed disproportionation of *cis*-Δ^4-cyclohexene-1,2-dicarboxylic acid (XXX) led exclusively to a monodecarboxylated aromatic product in accordance with the equation.



(XXX)

Similarly, transfer dehydrogenation of the acid (XXX) with *o*-nitrobenzoic acid as acceptor gave benzoic acid in 80% yield. Disproportionation of a variety of compounds related to XXX revealed a remarkable specificity. Both methyl and phenyl substitutents in the 3-position led to selective removal of the adjacent carboxyl group and

yielded *m*-substituted benzoic acids. Furthermore, 3,6-diphenyltetrahydrophthalic acid lost both carboxyl groups giving terphenyl and 3,6-diphenylhexahydrophthalic acid. Attempts to carry out transfer dehydrogenation of some of the substituted tetrahydro acids using *o*-nitrobenzoic acid or *p*-nitrotoluene as acceptors have so far failed, but it is likely that suitable acceptors could be found. Since the Δ^4-cyclohexene-1,2-dicarboxylic acid system is one which is readily constructed by a diene synthesis with maleic anhydride, this novel dehydrogenation becomes a potentially valuable method for the synthesis of *m*-substituted benzoic acids and of teraryls.

IV. Photochemical Hydrogen Transfer

Although typical donor-acceptor pairs often undergo photocatalyzed oxidation-reduction, the products are seldom those corresponding to simple hydrogen transfer. The photochemical process usually leads to coupling of the donor or acceptor or of both in a manner which is to some extent characteristic of reactions involving free radical intermediates. The classical studies of Ciamician and Selber provide one or two authentic examples of the transfer of pairs of hydrogen atoms from one molecule to another (101,102). Of these the photochemical oxidation of primary and secondary alcohols by quinones is the only general hydrogen transfer reaction. The mechanism of this process is now fairly well understood, and the principal reaction paths are as follows (103).

$$Q \xrightarrow{h\nu} Q^*$$

$$RR'CHOH + Q^* \rightarrow RR'\dot{C}OH + QH^\cdot$$

$$RR'CHOH + QH^\cdot \rightarrow RR'\dot{C}OH + QH_2$$

$$2QH^\cdot \rightarrow Q + QH_2$$

$$2RR'\dot{C}OH \rightarrow RR'CHOH + RR'CO$$

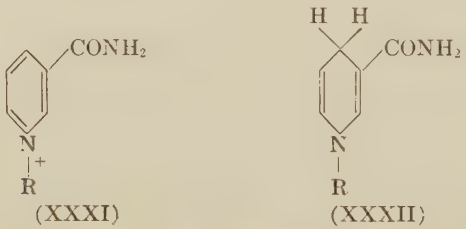
The excited quinone molecule (Q*) is a most undiscriminating reagent, and there is practically no difference in its rates of reaction with primary and secondary alcohols.

Although it is probable that photocatalyzed or photosensitized hydrogen transfer reactions are of great biological significance, it cannot yet be said that such processes are of much importance in organic chemistry.

V. Biochemical Hydrogen Transfer

Biochemists have long been preoccupied with hydrogen transfer reactions which constitute vital steps in the metabolism of all living matter. Some of the fruits of their labor have been handed on to the organic chemist, so that today increasing use is made of both *in vitro* and *in vivo* methods of oxidation and reduction. F. G. Fischer's excellent account of biochemical oxidation and reduction, as revised by Goddard and Stern in *Newer Methods of Preparative Organic Chemistry* (104), provides an admirable survey up to 1947. In spite of the fact that this extremely active field has been exhaustively reviewed since that time by *Annual Review of Biochemistry* and by reviews of many specialized individual topics, e.g., steroids (104a, 104b), any contemporary treatment of hydrogenation-dehydrogenation would be sadly incomplete if it did not include at least one or two recent examples of biological hydrogen transfer.

The great value of the biochemical method to the organic chemist is that it is usually completely stereospecific. The subtle and elegant uses which derive from this specificity are well illustrated by the brilliant researches of Westheimer and Vennesland which have culminated in the *in vitro* synthesis of optically pure (−)-ethanol-1-*d* in gram quantities (105). The reactions of a number of dehydrogenases and hydrogenases have been shown to involve the diphosphopyridine nucleotide (DPN$^+$, XXXI) as acceptor and its reduction product (DPNH, XXXII) as donor, respectively (106). These



(XXXI) (XXXII)

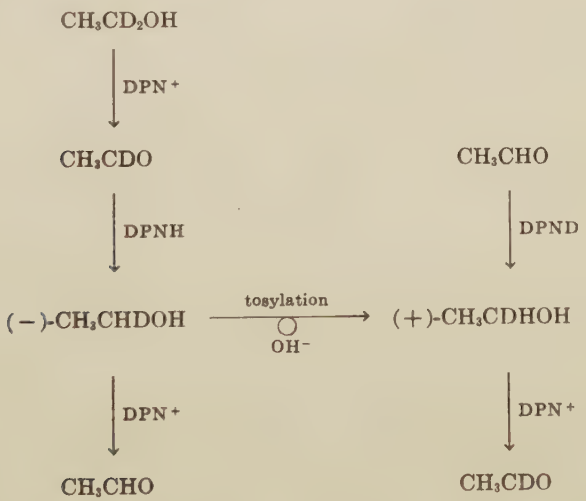
R = Ribose-pyrophosphate-ribose-adenosine

enzymes effect the direct transfer of one hydrogen atom between the nucleotide and the substrate. This has been demonstrated by deuterium-labeling experiments. Thus, yeast alcohol dehydrogenase catalyzes the exchange of deuterium from ethanol-1,1-d_2 to DPN$^+$ which can in turn transfer the deuterium to pyruvic acid in the presence of lactic dehydrogenase (107,108).

$$CH_3CD_2OH + DPN^+ \rightarrow CH_3CDO + DPND + H^+$$

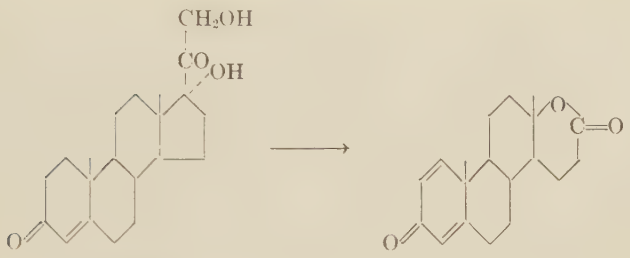
$$CH_3COCO_2^- + DPND + H^+ \rightarrow CH_3CD(OH)CO_2^- + DPN^+$$

That the reactions are also highly stereospecific is shown by the following transformations. Two samples of ethanol-1-*d* were prepared, one by the reduction of acetaldehyde-1-*d* with DPNH and the other by reduction of unlabeled acetaldehyde by DPND, both reactions being catalyzed by yeast alcohol dehydrogenase. These two alcohols were in fact diastereoisomers, as could be shown by their different behavior in transfer reactions with DPN^+. The alcohol derived from deuterated acetaldehyde was oxidized to deuterium-free acetaldehyde, whereas the other alcohol gave labeled acetaldehyde. Interconversion of the diastereoisomers could be achieved by alkaline hydrolysis of their *p*-toluenesulfonates. The reaction sequence is set out



schematically in Figure 2. These reactions, although proving the stereospecificity of the hydrogen transfer, are unsuitable for the preparation of optically active ethanol-1-*d* because they involve stoichiometric quantities of the very expensive nucleotide. This difficulty has been surmounted by using catalytic amounts of the nucleotide to effect an enzymic transfer of hydrogen from glucose to acetaldehyde-1-*d* (105).

$$CH_3CDO + \overset{\overset{\frown\!\!\!



(XXXV) (XXXVI)

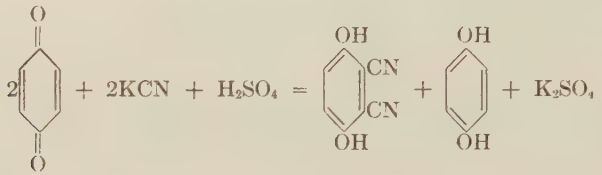
VI. Experimental Procedures for the Preparation and Use of High Potential Quinones

The three high potential quinones recommended in Section II-A-2 are not commercially available, and, since their preparations on an adequate scale are not satisfactorily described in the literature, details are given here.

Tetrachloro-1,2-benzoquinone is readily prepared from catechol (112,113). Chlorine is passed slowly through a stirred solution of catechol (200 g.) in glacial acetic acid (1 liter). The temperature of the mixture is maintained between 20 and 30°. After a period of time dependent upon the temperature and rate of passage of chlorine, tetrachlorocatechol separates and the mixture becomes semisolid. The solid is removed by filtration, and the filtrate is treated with chlorine until no more solid separates. After filtration, the solid is combined with the first crop and washed colorless with the minimum amount of acetic acid. This product (380 g., 84%) is sufficiently pure for the next stage. Tetrachlorocatechol forms a series of solvates with water and acetic acid, but a resublimed sample has m.p. 194°. The crude tetrachlorocatechol (340 g.) is dissolved in ethanol (500 ml.) and rapidly added to a vigorously stirred mixture of glacial acetic acid (720 ml.) and concentrated nitric acid. Some of the catechol separates during the addition but subsequently redissolves. When all the tetrachlorocatechol has been added, the mixture is stirred for 1 min. and then diluted with ice-cold water (2.5 liters). After the mixture has been allowed to stand for 10 min., the precipitated quinone is removed by filtration and dried in air. Tetrachloro-1,2-benzoquinone (220 g., 66%) has m.p. 128–130°. The melting point can be raised to 133° by recrystallization from benzene–light petro-

leum (1:5) or by sublimation, but the crude product is usually sufficiently pure for preparative purposes.

The key stage in the conversion of 1,4-benzoquinone to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is the initial formation of 2,3-dicyanohydroquinone which takes place according to the following equation (22).



The addition proceeds smoothly provided the temperature of the reaction is maintained within the limits prescribed by Allen and Wilson (114). 1,4-Benzoquinone (110 g.) is dissolved in ethanol (2.5 liters), and ethanolic sulfuric acid (25 ml. of concentrated acid in 100 ml. of ethanol) is added. The mixture is cooled to 20° and a saturated solution of potassium cyanide (70 g. of KCN) is added over a period of 4–5 hr. during which time the temperature is carefully maintained between 20 and 30°. The reaction is complete when the mixture is alkaline, at which stage it is brown in color and exhibits a green fluorescence. The mixture is made just acid (Congo Red) with concentrated sulfuric acid. At this stage the considerable quantity of potassium sulfate which separates is removed by filtration and thoroughly washed with hot ethanol. The combined filtrate and washings are evaporated to a small bulk (500–600 ml.) avoiding excessive and prolonged heating. On cooling, the solution deposits crude 2,3-dicyanohydroquinone which is collected and recrystallized (charcoal) from water. The pure crystalline material (55 g., 68%) exhibits a blue fluorescence in water and decomposes at 230°. The introduction of the two chlorine substituents is achieved in five steps which are: (*1*) oxidation, (*2*) hydrochlorination, (*3*) oxidation, (*4*) hydrochlorination, (*5*) oxidation. The oxidations involve the use of mixed nitrogen oxides (115) which are prepared by the action of arsenious oxide (300 g.) on a mixture of fuming nitric acid (250 ml.) and concentrated sulfuric acid (100 ml.). The red vapors which are evolved are condensed in a solid carbon dioxide–methanol trap. The liquid (90 ml.) thus obtained can be stored in a glass-stoppered bottle at 0°. Finely

powdered 2,3-dicyanohydroquinone (50 g.) is suspended in anhydrous carbon tetrachloride (750 ml.). Nitrogen oxides (22 ml.) are slowly added to the stirred suspension. After the addition is complete, the mixture is stirred for a further 5 min. The quinone is removed by filtration and washed with carbon tetrachloride. The product (44 g.) thus obtained is then suspended in chloroform (500 ml.) and treated with a rapid stream of anhydrous hydrogen chloride. Care must be taken to prevent the access of moisture. After 2 hr. the originally bright yellow quinone is converted to pale yellow granular 2-chloro-5,6-dicyanohydroquinone (53 g.), which is removed by filtration. The subsequent oxidations, steps (*3*) and (*5*), and the hydrochlorination, step (*4*), are carried out in the same way. Purification of the various intermediates is unneccessary and even undesirable, and the five stages can be completed in 1 day. However, incomplete removal of the reagents from the products of the intermediate stages usually results in the formation of a certain amount of dichlorodicyanobenzoquinone prior to the last oxidation. The final product is recrystallized from benzene–light petroleum (b.p. 60–80°). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone separates as red plates containing benzene of crystallization. The solvate decomposes in a vacuum desiccator to the solvent-free quinone (41 g., 57%), which is a bright yellow powder, m.p. 206–207°

The most difficult step in the synthesis of 3,5,3′,5′-tetrachloro-4,4′-diphenoquinone (116) is the preparation of 4,4′-dihydroxydiphenol. However, by using the method of Wilds, Shunk, and Hoffman (117) for this step, it is possible to obtain the desired quinone in a 20% yield from benzidine. Technical benzidine (200 g.) is dissolved in a hot mixture of concentrated hydrochloric acid (210 ml.) and water (2150 ml.). The solution is filtered hot and the filtrate cooled to 25° After the addition of a further quantity (235 ml.) of hydrochloric acid, the suspension is cooled to below 10° and a solution of sodium nitrite (151 g.) in water (450 ml.) added slowly with stirring. When the addition is complete, urea (1 g.) is added and the mixture stirred for a further 20 min. The solution of the diazonium salt is slowly added to hot (85–90°) aqueous sulfuric acid (215 ml. of conc. sulfuric acid in 4.3 liters of water). The mixture is stirred for 10 min., cooled, and filtered. The residue is crystallized once from ethanol (m.p. 240–241°) and then suspended in glacial acetic acid (500 ml.). Chlorine is passed through the suspension which at first

darkens and then, after 10 min., becomes homogeneous. At this stage tetrachlorodiphenol begins to separate and after a further 15 min. the reaction is complete. The product is removed by filtration and recrystallized from aqueous ethanol. The finely powdered tetrachlorodiphenol is dissolved in glacial acetic acid (3 liters) at 90°. Fuming nitric acid (6 ml.) is then added with vigorous stirring. The quinone immediately begins to separate as beautiful red plates (70 g., 20% from benzidine). After washing with light petroleum (b.p. 40–60°), the quinone is virtually pure and recrystallization from chlorobenzene does not alter its visible light absorption. The quinone decomposes at about 230°.

The preferred solvents for quinone dehydrogenation are benzene, chlorobenzene, or *o*-dichlorobenzene according to the desired operating temperature. It is important that these solvents be rigorously dried before use. The hydroquinones of dichlorodicyanobenzoquinone and tetrachlorodiphenoquinone separate quantitatively from the above solvents, and their formation during a reaction can be used as a rough gauge of the extent of dehydrogenation.

The conversion of 1,1-dimethyltetralin to 1,2-dimethylnaphthalene illustrates a convenient technique for small-scale quinone dehydrogenation. 1,1-Dimethyltetralin (2.1 g.), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.4 g.) and sodium-dried benzene (7 ml.) are heated in a sealed tube at 80° for 20 hr. It is necessary to shake the tube continuously during the first 5 min. to insure complete dissolution of the reactants. The intensely red solution fades as the reaction proceeds, and there is a continuous deposition of the hydroquinone. After cooling, the solid (3.6 g.) is removed by filtration and washed well with benzene. The combined filtrate and washings are then passed down a $9 \times {}^{3}/_{4}$ in. column of chromatographic alumina and the column eluted with benzene (100 ml.). The evaporated eluate and picric acid (1.6 g.) are dissolved in hot ethanol (12 ml.). On cooling the solution deposits orange needles which, when recrystallized from ethanol, afford pure 1,2-dimethylnaphthalene picrate (3.7 g., 76%), m.p. 131°.

Sealed tubes are not convenient for large scale reactions which may be conveniently carried out using conventional apparatus for anhydrous reactions.

References

1. E. A. Braude and R. P. Linstead, *J. Chem. Soc.*, *1954*, 3544.
2. A. L. Wilds in *Organic Reactions*, Vol. II, Wiley, Inc., New York, 1944, p. 178.
3. C. Djerassi in *Organic Reactions*, Vol. VI, Wiley, New York, 1944, p. 207.
4. L. M. Jackman and A. K. Macbeth, *J. Chem. Soc.*, *1952*, 3252.
5. E. Clar and Fr. John, *Ber.*, *163*, 2967 (1930).
6. J. Schmidt and A. Sigwart, *Ber.*, *46*, 1491 (1913).
7. E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, *1954*, 3548.
8. E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, *1954*, 3564.
9. R. P. Linstead, E. A. Braude, L. M. Jackman, and A. W. Beames, *Chem. & Ind.* (*London*), *1954*, 1174.
10. E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, *1960*, in press.
11. A. M. Creighton and L. M. Jackman, Unpublished results.
12. E. A. Braude, L. M. Jackman, and D. T. Thompson, Unpublished results.
13. L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, *77*, 6284 (1955).
14. O. Dimroth, *Angew. Chem.*, *46*, 571 (1933); *51*, 404 (1938).
15. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, *79*, 1913 (1957).
16. E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, *1954*, 3569.
17. R. Gaertner, *J. Am. Chem. Soc.*, *76*, 6150 (1954).
18. L. W. Butz and A. N. Rytina in *Organic Reactions*, Vol. V, Wiley, New York, 1949, p. 136.
19. E. Clar, *Ber.*, *64*, 1676 (1931).
20. D. Buckley and H. B. Henbest, *Chem. & Ind.* (*London*), *1956*, 1096.
21. W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Am. Chem. Soc.*, *80*, 2783 (1958).
22. J. Thiele and F. Günther, *Ann.*, *349*, 45 (1906).
23. L. Horner and H. Merz, *Ann.*, *570*, 89 (1950).
24. C. L. Jackson and R. D. MacLaurin, *Am. Chem. J.*, *37*, 7 (1907); *38*, 127 (1907).
25. G. O. Schenck, B. Brähler, and M. Cziesla, *Angew. Chem.*, *68*, 247 (1956).
26. W. J. Detroit, and H. Hart, *J. Am. Chem. Soc.*, *74*, 5215 (1952).
27. E. A. Braude, L. M. Jackman, R. P. Linstead, and J. S. Shannon, *J. Chem. Soc.*, *1960*, in press.
28. A. Schönberg and A. Mustafa, *Chem. Revs.*, *40*, 181 (1947).
29. N. Dost and K. Van Nes, *Rec. trav. chim.*, *70*, 403 (1951).
30. L. M. Jackman and J. W. Lown, Unpublished results.
31. G. Baddely and J. Chadwick, *J. Chem. Soc.*, *1951*, 368.
32. P. A. Plattner in *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., New York, 1948, p. 36.
33. This follows from the work of S. Winstein and his co-worker on neighboring-group effects, see A. Streitwieser, *Chem. Revs.*, *56*, 569 (1956).
34. G. Lowe, F. G. Torto, and B. C. L. Weedon, *J. Chem. Soc.*, *1958*, 1855.
35. W. A. Bonner and C. J. Collins, *J. Am. Chem. Soc.*, *75*, 5375 (1953).

36. B. M. Barclay and N. Campbell, *J. Chem. Soc., 1945*, 530.
37. Ng. Ph. Buu-Hoï, Ng. Hoán, and Ng. H. Khôi, *J. Org. Chem., 14*, 492 (1949).
38. W. Treibs, R. Steinert, and W. Kirchhof, *Ann., 581*, 54 (1953).
39. E. A. Braude, J. Hannah, and R. P. Linstead, Unpublished results.
40. L. M. Jackman and D. I. Packham, Unpublished results.
41. R. Bonnett and L. M. Jackman, Unpublished results.
42. U. Eisner and R. P. Linstead, *J. Chem. Soc., 1955*, 3749; U. Eisner, R. P. Linstead, E. A. Parkes, and E. Stephens, *J. Chem. Soc., 1956*, 1655; U. Eisner, A. Lichtarowicz, and R. P. Linstead, *J. Chem. Soc., 1957*, 733; U. Eisner, *J. Chem. Soc., 1957*, 3461.
43. J. H. Golden, R. P. Linstead, and G. H. Whitham, *J. Chem. Soc., 1958*, 1725.
44. G. E. Ficken, R. P. Linstead, E. Stephens, and M. Whalley, *J. Chem. Soc., 1958*, 3879.
45. M. A. T. Rogers, *Nature, 177*, 128 (1956).
46. H. Wynberg, *J. Am. Chem. Soc., 80*, 365 (1958).
47. R. T. Arnold and C. J. Collins, *J. Am. Chem. Soc., 61*, 1407 (1939).
48. E. E. van Tamelen and G. T. Hildahl, *J. Am. Chem. Soc., 78*, 4405 (1956)
49. A. I. Kosak and R. L. Holbrook, *Science, 177*, 231 (1953).
50. H. Wynberg, A. Logothetis, and D. Ver Ploeg, *J. Am. Chem. Soc., 79*, 1972 (1957).
51. Ng. Ph. Buu-Hoï, Ng. Hoan, Ng. H. Khôi, and Ng. D. Xuong, *J. Org. Chem., 14*, 802 (1949).
52. A. I. Kosak, J. F. Palchak, W. A. Steele, and C. M. Selwitz, *J. Am. Chem. Soc., 76*, 4450 (1954).
53. E. A. Braude, R. P. Linstead, and K. R. Wooldridge, *J. Chem. Soc., 1956*, 3070.
54. C. K. Warren and B. C. L. Weedon, *J. Chem. Soc., 1958*, 3972.
55. R. F. Brown and L. M. Jackman, *J. Chem. Soc., 1960*, in press.
56. E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc., 79*, 1258 (1957).
57. E. J. Agnello, Private communication.
58. E. Clar, *Ber., 69*, 1686 (1936).
59. C. Weizmann, E. Bergmann, and T. Berlin, *J. Am. Chem. Soc., 60*, 1331 (1938).
60. E. Bergmann, *J. Am. Chem. Soc., 64*, 176 (1942).
61. E. Bergmann, L. Haskelberg, and F. Bergmann, *J. Org. Chem., 7*, 303 (1942).
62. G. Swain and A. R. Todd, *J. Chem. Soc., 1942*, 626.
63. E. A. Braude and J. S. Fawcett, *J. Chem. Soc., 1951*, 3117.
64. K. Ziegler and H. Zeiser, *Ann., 485*, 174 (1931).
65. R. H. F. Manske and M. Kulka in *Organic Reactions*, Vol. VII, Wiley, New York, 1953, p. 59.
66. A. Kaufmann and H. Hüssy, *Ber., 41*, 1735 (1908).
67. J. A. Elvidge and F. B. Chapman, Unpublished results.
68. S. J. Angyal and R. C. Rassack, *J. Chem. Soc., 1949*, 2700.
69. P. J. McLaughlin and E. C. Wagner, *J. Am. Chem. Soc., 66*, 251 (1944).
70. K. Hess, *Ber., 46*, 4104 (1913).
71. K. Hess, F. Merck, and Cl. Uibrig, *Ber., 48*, 1886 (1915).
72. J. K. Simons, *J. Am. Chem. Soc., 59*, 518 (1937).

73. W. Traube and A. Engelhardt, *Ber.*, *44*, 3149 (1911).
74. M. Nakasaki, *J. Chem. Soc. Japan, Pure Chem. Sect.*, *74*, 403 (1953).
75. A. Michaelis, *Ber.*, *26*, 2162 (1893).
76. G. Baddeley and W. Pickles, *J. Chem. Soc.*, *1953*, 3726.
77. P. D. Bartlett and J. D. McCollum, *J. Am. Chem. Soc.*, *78*, 1441 (1956).
78. N. Zelinsky, *Ber.*, *58*, 185 (1925).
79. E. F. Armstrong and T. P. Hilditch, *Proc. Roy. Soc.* (*London*), *96A*, 322 (1919).
80. E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem.*, *13*, 455 (1948).
81. K. Ashida, *J. Agr. Chem. Soc. Japan*, *20*, 621 (1944); through *Chem. Abstr.* *44*, 7780 (1950).
82. C. Djerassi, A. J. Manson, and M. Gorman, *J. Am. Chem. Soc.*, *77*, 4925 (1955).
83. J. V. Karbinos and A. T. Ballum, *J. Am. Chem. Soc.*, *75*, 4501 (1953).
84. E. A. Braude, R. P. Linstead, and P. W. D. Mitchell, *J. Chem. Soc.*, *1954*, 3578.
85. E. A. Braude, R. P. Linstead, and K. R. H. Wooldridge, *J. Chem. Soc.*, *1954*, 3586.
86. E. A. Braude, R. P. Linstead, and K. D. E. Whiting, Unpublished results.
87. E. A. Braude, R. P. Linstead, P. W. D. Mitchell, and K. R. H. Wooldridge, *J. Chem. Soc.*, *1954*, 3595.
88. H. Adkins, L. M. Richards, and J. W. Davis, *J. Am. Chem. Soc.*, *63*, 1320 (1941).
89. H. Adkins, D. S. Rae, J. W. Davis, G. F. Hager, and K. Hoyle, *J. Am. Chem. Soc.*, *70*, 381 (1948).
90. H. Adkins and J. W. Davis, *J. Am. Chem. Soc.*, *71*, 2955 (1949).
91. H. Adkins and D. C. England, *J. Am. Chem. Soc.*, *71*, 2958 (1949).
92. H. Adkins and G. F. Hager, *J. Am. Chem. Soc.*, *71*, 2962 (1949).
93. H. Adkins and L. G. Lunstead, *J. Am. Chem. Soc.*, *71*, 2964 (1949).
94. E. C. Kleiderer *et al.*, *U. S. Dept. of Commerce Report, P.B. 981*, 1945; cf. ref. 80.
95. S. Pietra and G. Traverso, *Gazzetta*, *81*, 687 (1951).
96. W. E. Badcock and K. H. Pausacker, *J. Chem. Soc.*, *1951*, 1373.
97. S. Akabori and T. Suzuki, *Proc. Imp. Acad.* (*Tokyo*), *5*, 255 (1929).
98. S. Akabori and K. Saito, *Proc. Imp. Acad.* (*Tokyo*), *6*, 236 (1930).
99. S. Akabori and K. Saito, *Ber.*, *63*, 2245 (1930).
100. R. C. Elderfield and A. Maggiolo, *J. Am. Chem. Soc.*, *71*, 1906 (1949).
101. G. Ciamician and P. Selber, *Ber.*, *33*, 2911 (1900).
102. G. Ciamician and P. Selber, *Ber.*, *34*, 1530 (1901).
103. B. Atkinson and M. Di, *Trans. Faraday Soc.*, *54*, 1331 (1958).
104. *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., New York, 1948, p. 159.
104a. S. H. Eppstein, P. D. Meister, H. C. Murray and D. H. Peterson, *Vitamins and Hormones*, *14*, 359 (1956).
104b. E. Vischer and A. Wettstein, *Angew. Chem.*, *69*, 456 (1957).
105. R. H. Levy, F. A. Loewus, and B. Vennesland, *J. Am. Chem. Soc.*, *79*, 2949 (1957).

106. B. Vennesland, *Discussions Faraday Soc., 20,* 240 (1955).
107. H. F. Fisher, E. E. Conn, B. Vennesland, and F. H. Westheimer, *J. Biol. Chem., 202,* 687, 699 (1953).
108. F. A. Loewus, F. H. Westheimer, and B. Vennesland, *J. Am. Chem. Soc., 75,* 5018 (1953).
109. J. K. Grant, *Ann. Repts. on Progr. Chem. (Chem. Soc. London), 52,* 316 (1955).
110. E. Vischer and A. Wettstein, *Experientia, 9,* 371 (1953).
111. J. Fried, R. W. Thoma, and A. Klingsberg, *J. Am. Chem. Soc., 75,* 5764 (1953).
112. C. L. Jackson and R. D. MacLaurin, *Am. Chem. J., 37,* 7 (1907).
113. C. L. Jackson and P. W. Carlton, *Am. Chem. J., 39,* 493 (1908).
114. C. F. H. Allen and C. V. Wilson, *J. Am. Chem. Soc., 63,* 1756 (1941).
115. A. G. Brook, *J. Chem. Soc., 1952,* 5040.
116. E. Magatti, *Ber., 13,* 224 (1880).
117. A. L. Wilds, C. H. Shunk, and C. H. Hoffman, *J. Am. Chem. Soc., 76,* 1733 (1954).

ULTRAVIOLET PHOTOCHEMISTRY OF SIMPLE UNSATURATED SYSTEMS

By PAUL DE MAYO, *The University of Western Ontario, London, Canada*

CONTENTS

I. Introduction 367
II. Apparatus 369
III. Mechanism of Photochemical Reactions 371
IV. Monocarbonyl Compounds 372
V. Nonenolizable α-Diketones and Related Substances 383
VI. α,β-Unsaturated Carbonyl Compounds 387
A. Dimerization 387
B. Formation of Bridged Structures Containing a Cyclobutane Ring 390
C. Rearrangements 392
VII. Tropolones 398
VIII. Ethylenic Systems 399
A. Isomerization 399
B. Conjugated Ethylenic Systems 403
C. Aromatic Systems 407
IX. Diazoketones 407
X. Diazoalkanes 410
XI. Oxygen Transfer Reactions 411
A. Nitrone–Amide Rearrangement 411
B. Azoxybenzene–*o*-Hydroxyazobenzene Rearrangement 412
C. *o*-Nitrobenzaldehyde–*o*-Nitrosobenzoic Acid Rearrangement 412
XII. Miscellaneous Reactions 414
XIII. Experimental 415
A. Irradiation of 6-Methyl-6-acetoxycyclohexa-2,4-dienone 415
B. Preparation of Δ^2-Cyclohexenyldimethylcarbinol 415
C. Preparation of 2,6-Dimethyl-4-pyrone Dimer 416
References 416

I. Introduction

As early as sixty years ago it was appreciated that, apart from the biosynthetic processes involving chlorophyll and the chemical changes associated with vision, light could induce transformations in organic

compounds. Among the pioneers in this, the heroic age of photochemistry, were Ciamician and Silber (75) and Paterno (191). But despite the various and interesting discoveries made, the possibility of useful application (as distinct from chemical interest) of the knowledge accrued remained small. The reasons for this are manifold. First, light-induced processes, particularly those in which no chain reaction is involved, are expensive in terms of the energy input. Second, many light-induced reactions are initiated by the generation of radicals which are subsequently transformed. However, the selfsame radicals may frequently be made by other means, and more easily. The products of many photo-reactions may, in fact, be more readily available by normal chemical processes. Third, the products of photochemical reaction are frequently complex, and since the processes involved are not always well understood, control may be difficult. Finally, the availability of suitable light sources (other than the sun) and of related apparatus has, until recently, been limited.

But an apologia having been made, it remains a fact that preparative photochemistry has a place in general synthesis. We are at the beginning of a photochemical renaissance, and it is hoped that this survey, necessarily brief, will help to suggest the possible utility of photochemical processes when the opportunity should offer.

Photochemical transformation may be divided into several categories depending on the conditions of the operation. The light used may be ultraviolet or visible, and may be used with or without a sensitizer. Reactions may be induced in the vapor, the liquid, or even the solid phase, with notable differences in products. In addition, other physical factors such as temperature may be of importance, if not in the initial photochemical step, then in any of the immediately succeeding ones. The preparative aspects of such a vast subject cannot be adequately delineated here, and since the entire preparative field has recently been reviewed in a general sense (165,237), it is proposed herein to direct particular attention, for the main part, to ultraviolet-induced reactions in condensed phases in the absence of oxygen. Furthermore, those processes which depend for their inception primarily on a homolytic cleavage that may be induced in a facile manner by, say, peroxides will be mentioned more briefly or eschewed entirely.

Between the time of the origin of the study in Italy at the turn of the century and the recent revival with the work of Barton, Büchi, Schenk, Schönberg, and others, the examination of photochemical processes was almost entirely in the hands of physical organic chemists. The complexity of the reactions, notably in the gas phase, was such that despite a strong flow of papers clarification of details of the transformations was slow indeed; a recent review (93) of the photolysis of ketones lists over 50 papers on the photodecomposition of acetone without clear agreement (206) being achieved as to the details of modes (though not the products) of decomposition. Yet progress was at least sure, and with the advent of flash photolysis (41) it will be speedier. However, the plethora of results accruing from the endeavors of many organic chemists is highly suspect, partly because, in many instances, no controls were run, and in fact the reaction was induced by an agent other than light, and partly because the inadvertent presence of traces of impurities such as acids or peroxides may render the reaction irreproducible though light may be necessary for reaction. Such facts must be borne in mind in the interpretation of the literature.

II. Apparatus

The apparatus typically used in a photo-induced change consists of a light source surrounded by a transparent container. Provision may be necessary for cooling and agitation, and the material of the vessel may be glass or quartz depending on the wavelength of the light to be used. Pyrex, for instance, is useful down to about 3100 A. It is possible to devise apparatus of considerable complexity and varying efficiency, but on the other hand, the simplest apparatus will often serve. The entire subject has been discussed in detail (142,215) and here it will suffice to describe what is, for the types of reactions to be discussed, a bare minimum, but one which is, nevertheless, effective. Modification to achieve increased efficiency in terms of energy is not primarily the concern of the organic chemist whose immediate interest is the product.

First, it is, of course, essential that the light source should emit light in the region of absorption of the substance. The commonest sources are mercury arcs, and of these the medium-pressure are the most generally useful. The lines of the mercury spectrum produced which are relevant to likely absorbing unsaturated systems, and which

are the most intense, are those at 2537, 3126–3131, and 3650–3663 A.; the line at 2537 can be reversed by absorption of the radiation by the mercury vapor present in the lamp. Other bands are at 1840, 1942, 2652–2654, 2804, and 3021 A., and in the visible. For greatest efficiency the lamp may require some cooling with an airflow during running, but it should not be cooled below the maker's working temperature. High pressure arcs running at from a few to over 100 atmospheres are also available. At very high pressures the line reversal is intensified, and with further broadening of the lines the

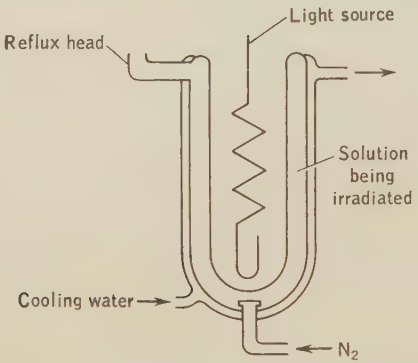


Figure 1

mercury spectrum appears against a continuum reaching from about 2700 A. The broadening lessens the intensity over a particular region, but of more practical importance to the occasional user is the fact that such lamps require much cooling and will break if the cooling is not maintained. Furthermore, operating at high pressures endangers the operators, and protection is necessary; this results in the complication of the apparatus with shields.

The apparatus indicated schematically in Figure 1 will be found adequate for most irradiations in the liquid phase. Lamps are commercially available which fit into the inner tube; it is possible to operate using commercial 125 watt light sources with the outer case removed, and compressed gas may be used as an additional cooling agent if the water-cooled outer jacket will not maintain the medium at the desired temperature. If higher temperatures are required, the jacket may be dispensed with, or the apparatus may be placed in a

cooling bath. Mixing can be achieved by passage of nitrogen (oxygen-free!) through the bubbler or by use of a magnetic stirrer.

It will be found that many of the transformations to be discussed can be achieved merely by setting the material to be irradiated in a quartz or glass flask, depending on the light to be absorbed, on a case containing the mercury arc. Mixing can be achieved with nitrogen, and cooling with a fan. The price to be paid may be simply time. Finally, small-scale transformations may be very simply achieved by irradiation under nitrogen in a closed quartz tube with a Pyrex seal (300). The tube is then cooled in a current of air. Care must, of course, be taken not to exceed the critical temperature. It will be noted that, on the whole, filters are not used in preparative ultraviolet photochemistry, but, on occasion, may be essential.

III. Mechanism of Photochemical Reactions

It is an elementary prerequisite that, for irradiating light to be effective, it must be absorbed. Einstein's law of photochemical equivalence states that one molecule reacts per quantum absorbed. However, in chemical practice it is found that there is a wide spectrum of values. Those where the quantum efficiency, that number of molecules reacting per quantum, is greater than unity are those where the light-generated species, or one formed from it, is self-perpetuating. Such would be the case where free radicals were generated which then initiated a chain reaction. On the other hand, the activated molecule may have alternative routes for disposal of the acquired energy, the quantum efficiency in any direction then being necessarily less than unity. Mechanistically the excited molecule, either in its original state or one formed from it by a radiationless transition, may dispose of this energy, with varying degrees of efficiency, by collision (thermally), homolysis, rearrangement, re-emission of light, etc., and the final product(s) may be derived by a very complex route. It would be inappropriate in an article of this kind to discuss these processes in any detail, especially since, except for the simplest instances, the intimate details are very far from well understood (37,202,207,239). However, in particular cases an attempt will be made to render the reaction intelligible from the organic chemist's point of view. It is not, of course, possible for a transformation to occur requiring more energy than that supplied by the light of the particular wavelength absorbed.

IV. Monocarbonyl Compounds

Simple ketones and aldehydes absorb with an extinction of 10–30 in the 290 mμ region and also at shorter wavelength. The former has been attributed to an $n \rightarrow \pi^*$ transition of a nonbonding electron on the oxygen atom. In the gas phase the photolysis of acetone results in the formation of ethane, carbon monoxide, and diacetyl (183). At temperatures above 200° ketene and ethylene are found. The production of these substances is contingent on the generation of methyl and acetyl radicals (179,182), and, indeed, the photolysis is used as a source of free radicals. Comparable results are obtained in the photolysis of aldehydes (32,164). Ketones having a side chain of more than three carbon atoms may decompose by another process giving rise to an olefin and a lower ketone, and a similar process has been proposed for aldehydes.

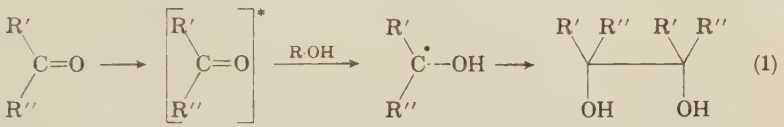
$$CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_3 \xrightarrow{h\nu} CH_3 \cdot CO \cdot CH_3 + C_3H_6$$

The suggestion made by Davis and Noyes (92; see also 180,181) that a six-membered cyclic mechanism (167) is involved has been interpreted in more detail (46,163) and appears very probable. (Experiments on deuterated 2-pentanone-1,1,1,3,3-d_5, however, suggest that more than one mechanism may be operative (313).) Furthermore, since the reaction is not inhibited by oxygen, it has been proposed that the singlet rather than the triplet state is involved (see, however, below).

The above decompositions, with the exception of those of the type of hexan-2-one illustrated above, are not of preparative significance, though they are of considerable interpretative value. Cyclic ketones have yet another process of photolysis in the vapor phase. As with the acyclic compounds, rupture occurs between the carbonyl carbon and the adjacent carbon, but, in part, a second rupture permits the formation of a biradical with the loss of carbon monoxide. This biradical may, by hydrogen transfer, give the olefin, or it may break down into smaller fragments; but an important course is the cyclization to give the cyclic hydrocarbon. Thus cyclopentanone gives ethylene and cyclobutane, the latter in 38% yield (38,148).

The reactions of aldehydes and ketones in the liquid phase, usually in a solvent (198), are of a different nature. Some of these parallel transformations in the aromatic series, and for simplicity the two

groups will be treated together. One of the most venerable of these reactions is the formation of pinacones by irradiation in alcoholic solution. This transformation, which has been known for over half a century (63,64) was first observed with aryl ketones, notably benzophenone, but the range has since been further extended (6,26,227,282). The reaction may be represented schematically as in equation 1. The



(1)

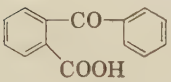
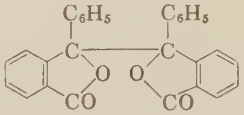
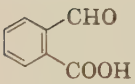
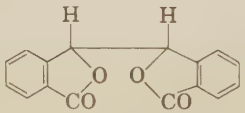
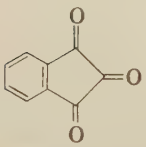
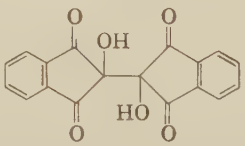
excited species indicated in brackets has been recently shown to be the triplet (311). It will be noted that the ketone is reduced at the expense of the alcohol.* It follows, therefore, that the aldehyde or ketone so produced may lead to mixed products (71,72,74). It is therefore desirable, where possible, to use the related alcohol. Some indication of the value of the reaction may be derived from Table I. The pinacol is not formed in all cases, for instance, from xanthone or fluorenone, and in fact if the pinacol from these substances, prepared by other means, is irradiated, the reaction is reversed (81,221). The reaction is independent of temperature in the range $-25°$ to $75°$, and water is a negative catalyst. Similar products have been reported from aldehydes (64); in these, as in much of the earlier work, sunlight was the irradiating source.

In the presence of alkoxides reduction to the benzhydrol rather than the pinacol takes place, and the yields on a number of substituted benzophenones are good. The intermediate formation of pinacols known to be decomposed by alkoxide, has been proposed, but does not appear to be necessarily involved (5). It is interesting that closely similar Oppenauer-type oxidation-reductions have been achieved *without* the intervention of light (290).

A number of related reactions have been reported in solvents other than alcohol, but in these cases an important photochemical step appears to be that carbon cleavage adjacent to the carbonyl group already noted. This is true, for instance, of certain benzyl ketones, such as deoxybenzoin which gives, among other products, dibenzyl,

* In the *total* absence of oxygen the mechanism may be modified, colored intermediates having been observed (199).

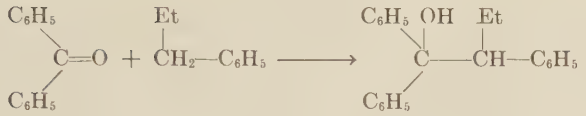
TABLE I[a]

Carbonyl compound	Alcohol	Product	Yield,[b] Light	%	Ref.
Acetone	Isopropanol		UV	—	215
Benzophenone	Benzhydrol		Sun	80	220
Benzophenone	Isopropanol		Sun	93	6
Acetophenone	Butanol		UV	—	29
p,p'-Dimethoxybenzophenone	Isopropanol		Sun	—	34
p,p'-Dichlorobenzophenone	Isopropanol		Sun	—	34
m-Phenylbenzophenone	Isopropanol	The related pinacol	Sun	55	35
Deoxybenzoin	Isopropanol		Sun	80	29
α-Tetralone	Isopropanol		Sun	75	30
Benzaldehyde	Ethanol		Sun	—	35
Anisaldehyde	Ethanol		Sun	—	35
$C_6H_5 \cdot CO \cdot COOH$	Isopropanol		Sun	—	232
	Ethanol		Sun	—	158
	Isopropanol		Sun	—	174
	Isopropanol		Sun	—	222

[a] No reaction was obtained with fluorenone, xanthone, α-naphthyl phenyl ketone, di-α-naphthyl ketone, and other substances.

[b] The yield is based on ketone. In many cases yields might be increased by prolonged irradiation.

benzaldehyde, and didesyl. It has been noted, however (141,235), that where a hydrogen atom may be removed by the activated carbonyl group to give a new stable radical, alternative paths are available. Reactions 2 and 3 are typical (73,193), and similar prod-

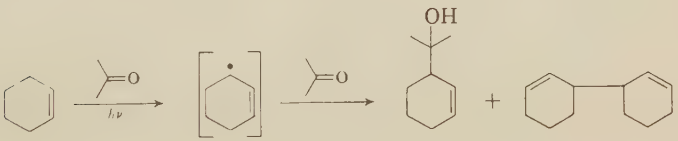


(2)

(3)

ucts are derived from xanthone and xanthene. Xanthene and acetophenone, however, are reported to give a mixture of tetraarylethane and the pinacol (25,178,184,221).

It has recently been found that allylic hydrogen is reactive under these conditions: irradiation of cyclohexene in acetone, diethylketone, or dipropylketone in the absence of oxygen gives the corresponding carbinol (equation 4) the derivative from acetone being obtained in at least 30% yield (301). A comparable transformation



(4)

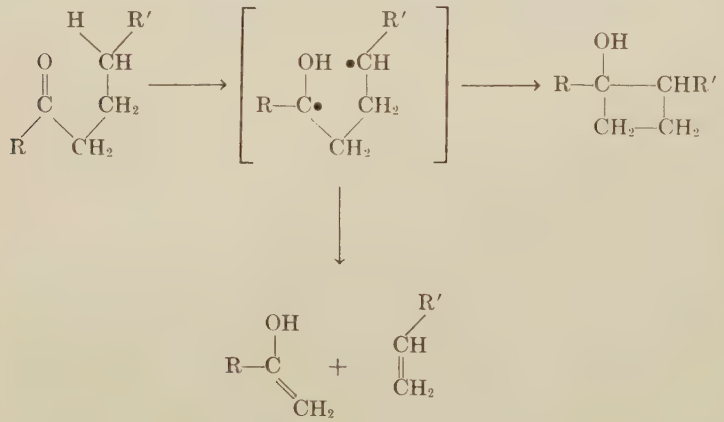
has been observed with cyclohexene and propionaldehyde, the expected secondary alcohol being among the products (301). An alternative reaction path involving attack of the double bond, rather than the allylic hydrogen, with subsequent loss of a β-hydrogen atom to form a new ethylenic linkage, has been excluded by comparable experiments on dihydrolimonene. The dihydrolimonene recovered after interruption of the irradiation before completion was partly recemized, indicating the intermediacy of a symmetrical allylic radical.

Even saturated hydrocarbons are attacked by the activated carbonyl group (36,293),* and from cyclohexane and acetone is obtained

* This is paralleled somewhat by the attack of hydrocarbons by the NO and Cl radicals produced by the irradiation of nitrosyl chloride (323).

cyclohexyldimethylcarbinol (12%) together with isopropanol (53%), pinacol (15%), and acetonylacetone. It is interesting that the free radical addition of formaldehyde to cyclopentane and cyclohexane has also recently been reported in 21.4 and 38% yields, respectively (110). No extensive photo-induced experiments have yet been reported to indicate the selectivity of carbonyl attack on hydrogen attached to primary, secondary, and tertiary carbon.

With ketones having side chains possessing γ-hydrogen the decomposition, favored in the gas phase, to a lower ketone and olefin occurs; but in addition, an intramolecular attack of the carbonyl carbon on the γ-carbon atom leads to the formation of cyclobutanols (239) The initiating step in both these reactions may be the same, namely, attack of the excited oxygen atom on the γ-hydrogen, the products then arising from alternative paths of decomposition of the incipient biradical (equation 5): both steps may, of course, be concerted, and it is in accord with this that the olefin is homogeneous, but recent work by Yang (324) supports a stepwise mechanism. Thus

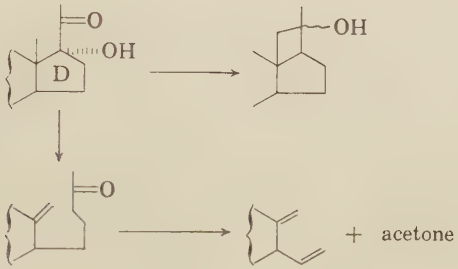


(5)

octan-2-one originally reported to give 67% acetone and 17% 1-methyl-2-propylcyclobutanol has now been shown to give isomeric cyclobutanols. Nonan-2-one gives 10% of the corresponding cyclobutanol. Although the yields are low, the method is so simple that it will undoubtedly take its place as a useful synthesis.

The attack of hydrogen on unactivated carbon in sterically restricted systems has been achieved recently by chemical means

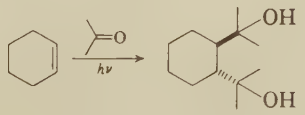
(53,85,86,115). The above-described reaction of ketones has also been applied in this context by two groups of workers (324,325), one of which has shown, again, that epimeric alcohols are produced. In addition, cleavage products, expected of ketones possessing γ-hydrogen atoms (see page 372), have also been found. An example is illustrated in scheme 5a. Further examples, recently reported, of photo-



(5a)

chemically induced attack on a suitably disposed hydrogen atom have been stated to occur in medium-sized rings, where the transannular proximity of the hydrogen atom in cyclodecanone leads to the formation of 9-hydroxy-*cis*-decalin in 35% yield (12), and cyclooctanone gives *cis*-bicyclo[3.3.0]octan-1-ol (324).

Aldehydes and ketones may also undergo addition reactions with olefins, but it is not yet clear in any particular situation why one or more of a number of possibilities obtain. Cyclohexene with acetone at temperatures higher than the optimal for production of the cyclohexenylcarbinols gives, as an additional product, the dicarbinol (I).

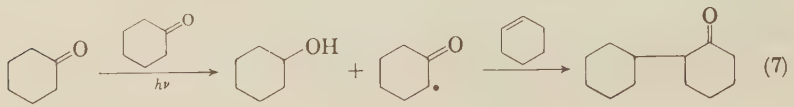


(6)

(I)

The yield of this product appears unaffected by the presence of oxygen, suggesting the nonintermediacy of a cyclohexenyl radical. If this is a molecular addition, the oxetan may be an intermediate in its formation (166). Cyclohexanone, however, does not, perhaps for steric

reasons, appear to give the same type of product. It affords, conceivably by the sequence of equation 7, cyclohexylcyclohexanone (166).



(7)

This transformation is analogous to the addition reaction observed by Kharasch and others with aldehydes and olefins. It has been proposed that the latter is a chain reaction involving the radical $\dot{R}CO$ (equation 8) (143,146), a scheme that allows for the formation

$$R\cdot\dot{C}O + R'CH{=}CH_2 \longrightarrow R'\dot{C}H\cdot CH_2\cdot COR$$

$$R'\dot{C}H\cdot CH_2\cdot COR + RCHO \longrightarrow R'CH_2\cdot CH_2\cdot COR + R\cdot\dot{C}O \quad (8)$$

of alkane and carbon monoxide as by-products. The formation of the acyl radical was originally postulated as being derived by photolytic cleavage of the C—H bond. An alternative process which has been proposed requires that the original photolytic cleavage be at the C—C bond (as in ketones) thus:

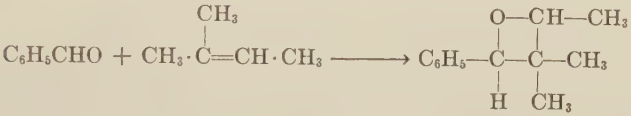
$$R\cdot CHO \longrightarrow R^{\bullet} + \dot{C}HO$$

$$R^{\bullet} + RCHO \longrightarrow RH + \dot{R}CO \quad (9)$$

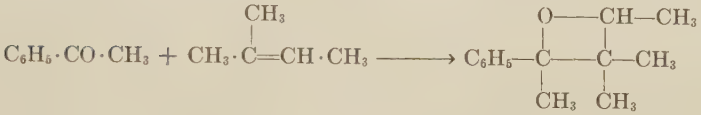
This reaction has been applied to the addition of long chain aldehydes to long chain 1-alkenes; and among the ketones synthesized are decan-2-one, cyclohexyl-1-heptanone, dodecan-4-one, and pentadecan-7-one.

A reported reaction apparently related to equation 4 is the transformation of citronellal to isopulegol (34). In view of the supposed accompanying racemization at a remote carbon atom the reaction has been reinvestigated. The isopulegol formed was said to be characterized as the semicarbazone of the derived ketone, and upon the melting point of this depended the claim of racemization. However, the semicarbazone is that of methone, and indeed the cyclization can proceed under conditions closely similar to those described by the authors, but in the absence of light (166).

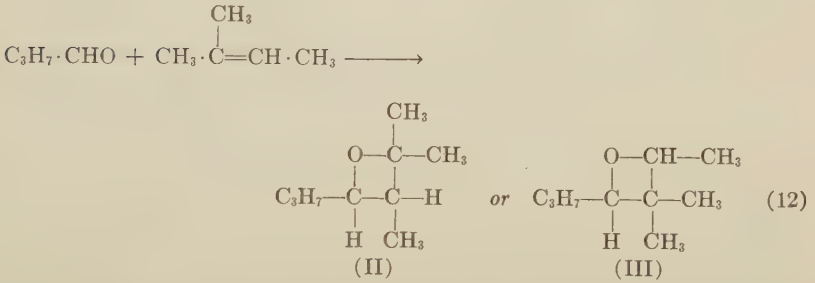
Another addition reaction of aldehydes and ketones, both aliphatic and aromatic, is that leading to the formation of trimethylene oxides. This was originally reported by Paterno (192) who stated that these substances were formed when mixtures of tri- and tetrasubstituted olefins and the carbonyl compounds were exposed to sunlight. This reaction has been reinvestigated recently by Büchi and his collaborators (47) with the results summarized in equations 10–12.



(10)



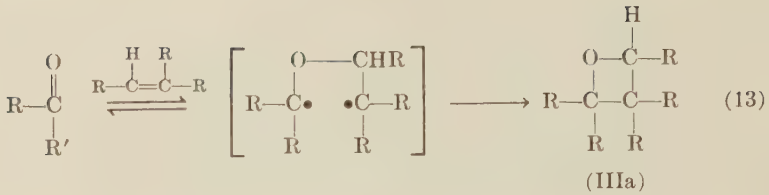
(11)



(12)

Two general questions are raised by these results: (*1*) Under what circumstances does Kharasch addition with aldehydes or a substitution reaction with ketones and aldehydes supplant the trimethylene oxide formation? (*2*) Granted oxide formation, what determines the direction and stereochemistry of addition to an unsymmetrical olefin?

If the lifetime of the excited molecule is such as to allow collisional reaction with the hydrocarbon to precede homolytic dissociation, then the course of the reaction will depend on the stability of the reversibly formed intermediate. With heavily substituted ethylenic linkages attack at the oxygen atom (from which a nonbonding electron has been promoted) in a Markownikoff sense gives the more stable biradical (equation 13).



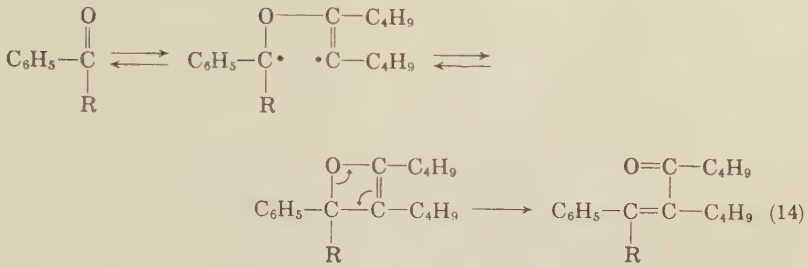
(13)

(IIIa)

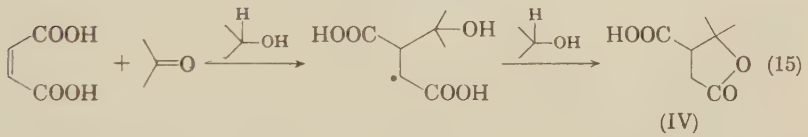
This rationalizes the direction of closure of two of the above oxides,* and predicts IIIa for that from butyraldehyde. In cases where the intermediate biradical is insufficiently stabilized by substitution (as with long chain terminal alkenes and in cyclohexene) Kharasch addition may take place. Alternatively, attack of some activated hydrogen, as in the carbinol formations, may occur. The above considerations are speculative, since the same route need not necessarily be followed by aldehydes and ketones, aliphatic or aromatic. The nuclear magnetic resonance spectrum of the products derived from butyraldehyde and from deuterobutyraldehyde indicates the presence of two and one hydrogen atoms, respectively, attached to carbon-bearing oxygen and thus supports structure III (51a) and, therefore, the general process indicated. Structure III has been entirely confirmed by a study of the fragmentation pattern in the mass spectrometer (51b).

The addition of carbonyl compounds to acetylenes has been investigated but little. The product is not the unsaturated trimethylene oxide, but may be derived from it. In the addition of benzaldehyde to dibutylacetylene the product is benzylidenedecan-5-one in 13% yield (49). From acetophenone and the same hydrocarbon the equivalent product was obtained in unspecified yield. The related peroxide-induced addition (217) leads to 1,4-diketones, and so the present instance is an interesting example wherein the two methods may lead to different results. Furthermore, the intervention of the acyl radical has been supposed in the peroxide-induced diketone formation, requiring, therefore, a different process to be followed for the photo-induced transformation. As a parallel to that postulated for the oxetane formation, the process has been rationalized as equation 14.

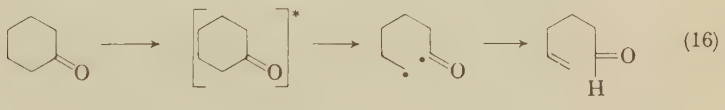
* The photolysis of oxetanes requires light of short wavelength (315).



The addition of a saturated carbonyl compound to a conjugated ethylenic linkage appears not to have been extensively investigated. A recent elegant application of this has been recorded by Schenk and his collaborators These workers achieved the addition of acetone (in a manner similar to the bis addition of this substance to cyclohexene) to maleic acid with the formation of terebic acid (IV); the reduction was effected by isopropanol present (216).



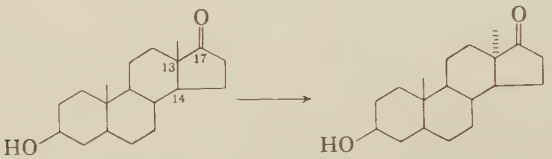
Cyclic ketones undergo an additional and apparently general reaction. This is cleavage to give the unsaturated aldehyde (312). Cyclohexanone, for instances, gives, among other products, hexenal (equation 16) (68,70,76,146); an intermediate biradical has been



postulated (10,24,210). It is not known whether the β-hydrogen transfer is inter- or intramolecular. This reaction may constitute an example where the same products are not obtained by free-radical-inducing reagents. However, in the case of cyclopentanone, allylacetaldehyde has been isolated among the products of reaction with acetylperoxide. The equivalent photoreaction has been reported for a bridged ketone, camphor (V), campholenaldehyde (VI) being among

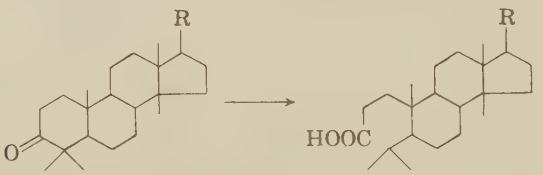
(V) (VI) (17)

the products (72). As evidence that biradicals of the kind illustrated are involved, conversions such as that of androsterone to lumiandrosterone may be cited, an inversion (equation 18) which must surely involve cleavage between C-13 and C-17 and not between C-13 and C-14 (14,30,35,56).



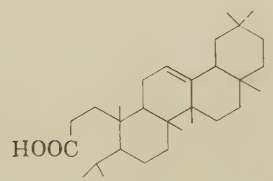
(18)

In the presence of water hydrolytic cleavage of such ketones occurs in addition to that of aldehyde formation. Cyclohexanone gives, for instance, caproic acid (68,76). It is to be expected that cleavage would occur on the side of the carbonyl to give the more stable biradical. That this is so has been shown in the hydrolytic cleavage of lanostanone (VII), which gives the primary acid. The process has been utilized in the synthesis of dihydronyctanthic acid (VIIa) and in the elucidation of the structure of dammarenolic acid (303). Reactions in the presence of oxygen are more complex (134).



(19)

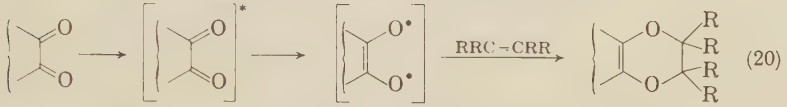
(VII)



(VIIa)

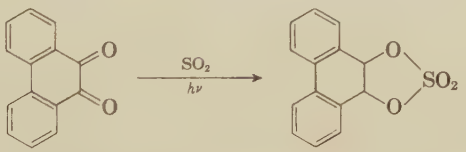
V. Nonenolizable α-Diketones and Related Substances

Nonenolizable α-diketones and *o*-quinones have been investigated extensively, but only under a few conditions. That of the most general nature is the reaction with olefins, and the over-all transformation may be represented as in equation 20 (57,227,228,229,232). The



(20)

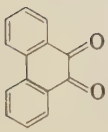
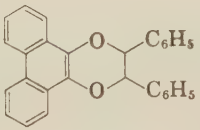
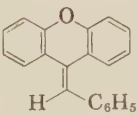
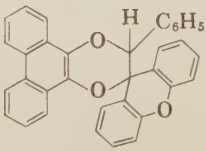
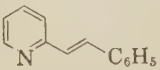
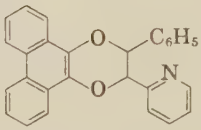
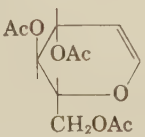
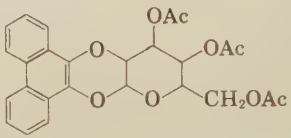
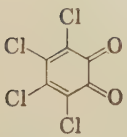
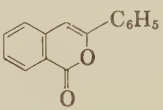
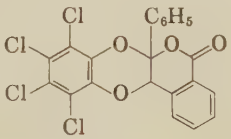
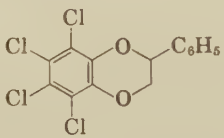
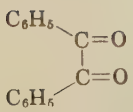
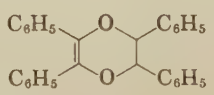
products are dioxanes. Among diketones which have been found to be active are benzil, *p,p'*-dianisil, *o*-benzoquinone, naphthoquinone, phenanthraquinone, and derivatives of certain of these substances. The olefin moiety may be open chain or part of a ring (175) and in most cases, though not all (122), is conjugated with at least one aromatic ring. In some cases, with very reactive quinones (174,231), the same reaction may proceed by heating in the dark, whereas in others a different reaction (123,233), e.g., Diels-Alder addition to the diene system, takes place. Thus, though excitation removes the barrier to reaction, with such large molecules the relationship between excited states and reactant-product energy contours is so complex it is not possible to predict whether the photoreaction product will be the same as the thermal one. Some idea of the scope of the reaction will be gained from Table II. Sulfur dioxide will also add to *o*-quinones giving cyclic sulfates, again in the manner of a photochemically induced Diels-Alder reaction (213).

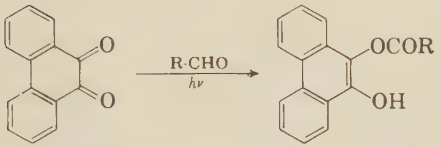


(21)

As long ago as 1888 *o*- and *p*-quinones were recorded as reacting photochemically with aldehydes (149) to give adducts of type VIII. The reaction has been further developed more recently (219,232), and the alternative structure (IX) proposed. However, since it has been shown that *p*-quinone also undergoes this reaction and, more important, that spectral evidence (172) is clearly in favor of the original proposals, structure VIII must now be accepted. It has

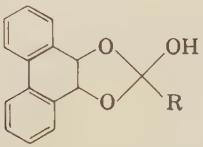
TABLE II
Ethylenic Addition Products with α-Diketones

Diketone	Ethylenic compound	Product	Ref.
	$C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5$		223
			173
			225
			122
			232
	$C_6H_5{\cdot}CH(CH_3){\cdot}CH{=}CH_2$		232
	$C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5$		225



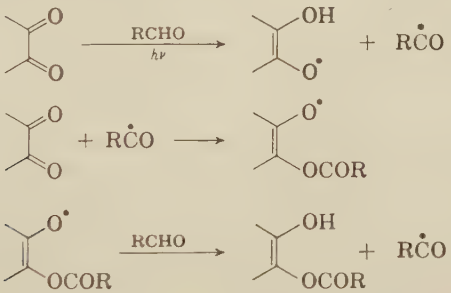
(22)

(VIII)



(IX)

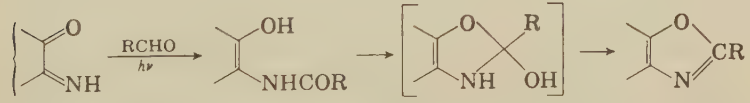
been proposed that this reaction is free radical in nature, proceeding as shown by equation 23, a process rationalizing the high quantum



(23)

yields said to be obtained. Some examples of this reaction and of that with *p*-quinone are illustrated in Table III. The yields are, in general, good.

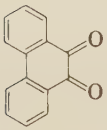
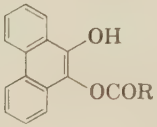
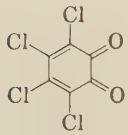
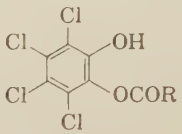
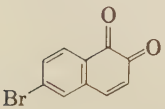
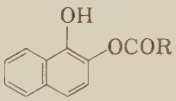
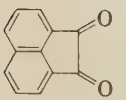
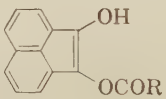
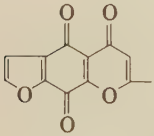
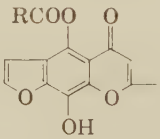
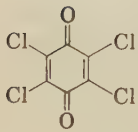
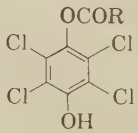
The addition of aldehydes to quinone imides has been accomplished (224), the intermediate amides readily being converted to oxazoles (equation 24). In the case of phenanthraquinone imide a number of



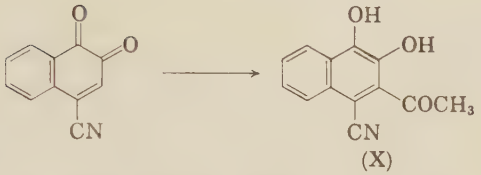
(24)

aldehydes have been employed with success. It is said that the same products are obtained using the oxime, a higher temperature being required for oxazole formation (177,230).

TABLE III

Quinone	Aldehyde, R·CHO	Product	Ref.
	R = C_6H_5· *p*-Cl·C_6H_4·		219
	R = CH_3· C_6H_5· *p*-CH_3·C_6H_4· C_6H_5·CH=CH·		232
	R = C_6H_5· *p*-CH_3·C_6H_4· *o*-MeO·C_6H_4· *o*-Cl·C_6H_4·	 (or isomer)	178
	R = C_6H_5· *p*-MeO·C_6H_4· C_6H_5·CH=CH· *o*-HO·C_6H_4·		241
	R = C_6H_5·		236
	R = C_6H_5·		172

In a few cases addition products other than those described above have been encountered. Thus 4-cyano-1,2-naphthoquinone is said to give with acetaldehyde a methyl ketone (X) (234), although with



(X) (25)

anisaldehyde the more normal course is followed. An addition process has also been recorded for the reactions of *p*-benzoquinone with acetaldehyde, with isovaleraldehyde, and with benzaldehyde and may well be the general reaction when no blocking groups are present to prevent aromatization (cf. Table III) (149).

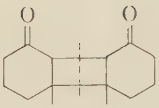
VI. α,β-Unsaturated Carbonyl Compounds

The transformations undergone by saturated and aromatic carbonyl compounds do not, in general, occur in α,β-unsaturated systems, presumably because more facile alternative paths are available. Of the transformations observed in the latter the most common is that of geometrical isomerism about an ethylenic linkage. However, since such isomerism occurs in other absorbing systems as well, discussion will be deferred until later (page 399). The interaction of the electrons of the double bond with those of another unsaturated system, with formation of two new carbon-carbon bonds, is also a common reaction path. The simplest manner in which this can occur is when two like molecules interact, that is, in dimerization.

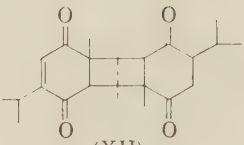
A. DIMERIZATION

The phenomenon of dimerization is well established in photochemistry, one of the oldest examples being that of a noncarbonyl compound, anthracene* (2,105,114,320). But, apart from anthracene and related compounds and a few other substances (318), most examples of dimerization have been reported from α,β-unsaturated carbonyl compounds and related species (176). As examples of this type of reaction may be quoted the dimerization of 3-methylcyclohexenone (XI) (267), of thymoquinone (XII) (295), of coumarin (XIII) (136), and of Δ^4-3-ketosteroids (XIV) (57).

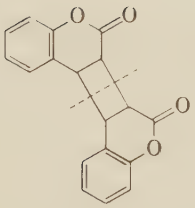
* The dimerization of anthracene-9-aldehyde has been shown, in an ingenious manner, to be head-to-head (114) by the use of anthracene-9-carboxylic acid anhydride, but other derivatives dimerize differently and the situation is not entirely clear.



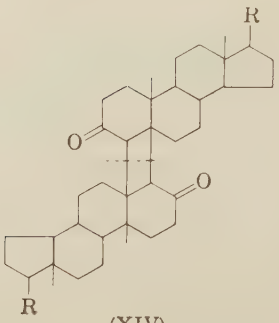
(XI)



(XII)

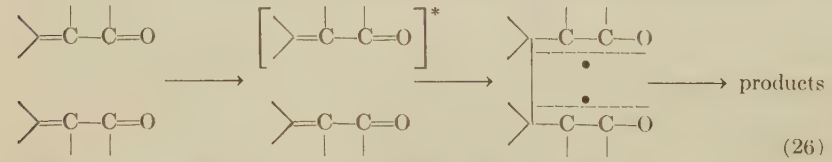


(XIII)



(XIV)

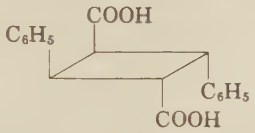
Two significant points are as yet unanswered with regard to the structures of all these substances. First, it remains to be established whether, in such systems as the question is meaningful, the carbonyl groups are *syn* or *anti* about the cyclobutane ring. Second, it is not known whether, in the product, substituents are on the same or on opposite sides of the plane of the cyclobutane ring. In a few particular cases these questions have been solved, but no generality has yet been established and no simple one may exist. In view of the product obtained from 2,6-dimethyl-4-pyrone (see equation 27) it could be supposed that *anti* addition might be the rule (and in the case of the steroid (XIV) this would surely avoid considerable strain). The opposite or *syn* mode, on the other hand, has the attraction that the more stable biradical is generated, assuming a radical process for the transformation. A further indication that conclusions should not be



(26)

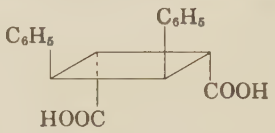
drawn by analogy in individual cases may be taken from the study of the dimerization of the cinnamic acids and of the chalcones. Here it has been found that the *physical state* of the material being irradiated

is of much importance. Thus slowly recrystallized *trans*-cinnamic acid gives α-truxillic acid (XV), whereas the metastable form of the *trans* acid gives β-truxinic acid (XVI) (28). (In the older literature varying amounts of the two isomers were reported.) Finally, *cis*-cinnamic acid gives mainly β-truxinic acid. Irradiation of cinnamic acid in solution, however, leads largely to isomerization about the



(XV)

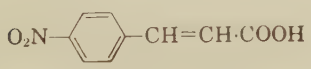
α-Truxillic acid



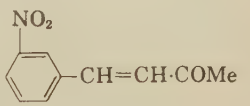
(XVI)

β-Truxinic acid

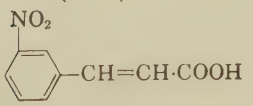
double bond. It would thus seem that orientation in the crystal lattice is of primary importance, though this in itself cannot provide the complete answer (205). Since these reactions are at least thermally reversible, the products isolated may not be the initial ones (247), and in some cases cleavage of the cyclobutane ring in another sense could be envisaged. However, the cyclobutane derivatives are *not* intermediates in the isomerization of *trans* to *cis* products (316). Furthermore, both isomers will not absorb light of the same wavelength with equal efficiency, and it is interesting that it has been reported that solid chalcone, when irradiated, gives both truxinic and truxillic dimers, the yield of the latter decreasing with decrease in wavelength of the light used (248). Such factors may conceivably account for the fact that XVII and XVIII are reported to be dimerized easily, but that XIX and XX are not (266).



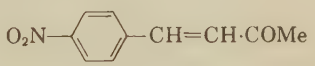
(XVII)



(XVIII)



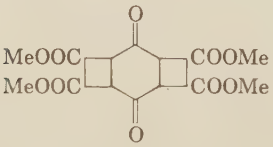
(XIX)



(XX)

In those cases where dimerization does take place in solution the products may or may not differ from those obtained in the solid state (84,294).

The dimerization of dienones has been reported, apparently, in two cases. The acyclic dimethyl-3-ketopentadienedicarboxylate has been described as giving a tricyclic product (XXI), although XXII does not behave in this way.

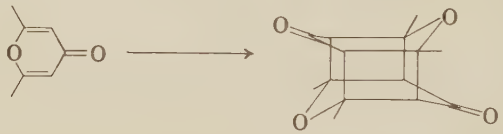


(XXI)

$C_6H_5{\cdot}CH{=}CH{\cdot}CO{\cdot}CH{=}CH{\cdot}C_6H_5$

(XXII)

The irradiation of 2,6-dimethyl-4-pyrone in the solid state (118,194) has been shown to involve dimerization on both ethylenic linkages (equation 27) (294) (see Section XIII), and in this instance the orientation of the carbonyl groups has been established by degradation.



(27)

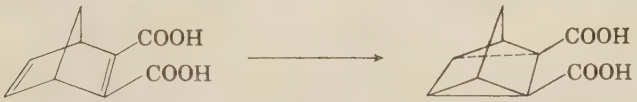
Irradiation in solution leads to a poor yield of the same product and in this case, at least, it is not merely the packing in the crystal which has directed orientation. Very recently the similar dimerization of benzoquinone derivatives has been reported, but here irradiation in solution does not give the same product; instead the normal unsaturated dimer is formed (84).

B. FORMATION OF BRIDGED STRUCTURES CONTAINING A CYCLOBUTANE RING

In the examples of dimerization of α,β-unsaturated carbonyl compounds quoted both ethylenic linkages were necessarily photochemically capable of activation, though it does not follow that *both* need to be activated for dimerization to occur. More recent studies have revealed that the requirements of such reactions are not so stringent as might have been imagined. Two factors appear necessary: (*1*) an ethylenic linkage capable of being activated by the light used and (*2*) a nearby, but not necessarily activated, double bond. The fact that such reactions lead to strained bridged systems not always available by

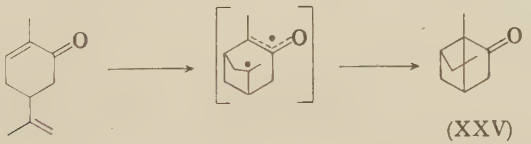
normal synthetic routes makes this group of particular interest to organic chemists.

One of the first of such transformations to be observed in a rigid system was the conversion of XXIII to XXIV, a reaction which is, as appears to be the general rule, reversed by heat (87). The homo-allylic participation of such bonds in solvolytic and other reactions is



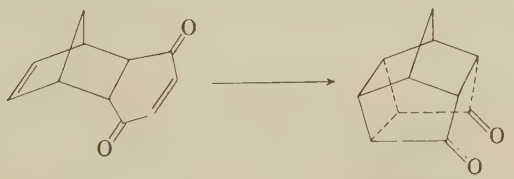
(XXIII) (XXIV)

well known from the work of Winstein and others, and the ready electronic interaction may be envisaged. But such is not the case in the formation of carvone camphor (69), yet this, probably the first of this class of substances to be made, has been shown recently (50) to have the structure XXV. Again, if an intermediate diradical is assumed, the product formed is that derived from the more stable of the alternative processes. Recently examples have been recorded



(XXV) (28)

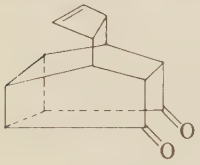
among the *endo* Diels-Alder products from 1,3-dienes. The adduct, for instance, of cyclopentadiene and benzoquinone on irradiation is transformed into a "cage" isomer (XXVI), a similar reaction taking place with the hexachloro derivative. XXVII, a hexacyclic ketone, was obtained by the irradiation of the adduct of cyclooctatetraene and benzoquinone (82). It has been suggested that the



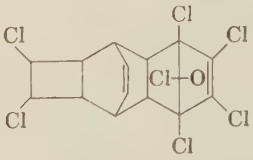
(XXVI) (29)

reaction might be of use in allocating configurations. Dichlorobicyclooctadiene adds hexachlorobicycloheptadiene to give two

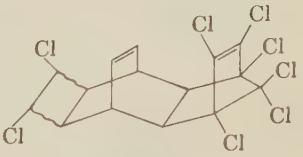
stereoisomers of structure XXVIII. Of the four possibilities the two



(XXVII)



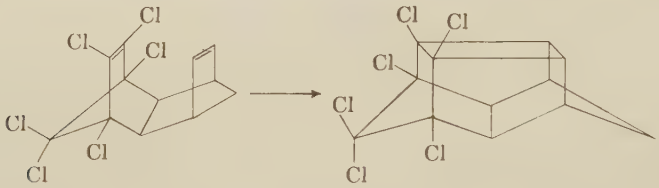
(XXVIII)



(XXVIIIa)

actually produced should be the pair XXVIIIa with the adjacent ethylenic linkages, since both are converted into photoisomers; the structures of these isomers, though probable, do not appear to have been established.

In the last example the photochemical change was induced in the *absence* of a carbonyl group. Another such case has been reported in the isomerization of the insecticide isodrin (equation 30) (83).



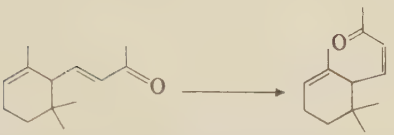
(30)

C. REARRANGEMENTS

This section includes some of the most interesting and unusual of photochemical transformations, but a detailed knowledge of the reaction path involved is often minimal. There are few rearrangement products of simple α,β-unsaturated ketones recorded. The unsaturated ketone verbenone (XXVIIIb) on irradiation does not, apparently, dimerize, but undergoes rearrangement to chrysanthenone ("carene oxide") (308).

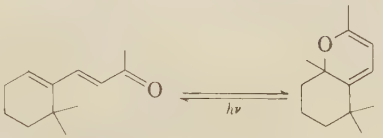
(XXVIIIb)

The irradiation of *trans*-α-ionone gives, as might be expected (see page 399), the *cis* product (equation 31). Similar irradiation of



(31)

trans-β-ionone (XXIX) gives, not the *cis* derivative, but the derived pyran (equation 32) (48). This reaction is reversible and the reverse



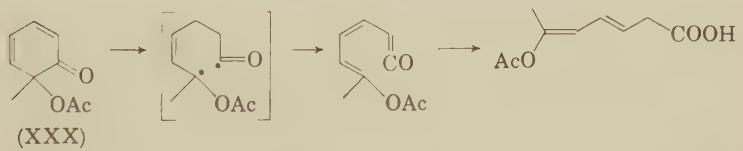
(32)

(XXIX)

reaction may be represented in general terms by equation 33.

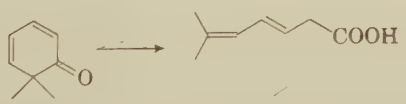
(33)

Other analogous reactions have since been recorded, and important among these are the photochemical hydrolyses of various cyclic dienones. Irradiation of these in wet ether (see Section XIII) leads to the formation of a number of unsaturated acids of synthetic utility. It is probable that an intermediate ketene, possibly derived from an initial diradical, is involved. As evidence for the intermediacy of a ketene it has been reported that irradiation of XXX in dry ether in the presence of aniline leads to the formation of the anilide in 79%

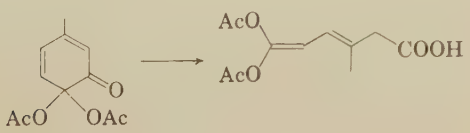


(34)

(XXX)



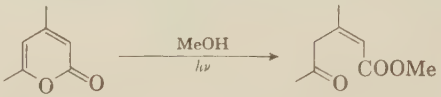
(35)



(35a)

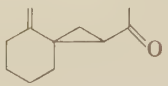
yield (20,21). In certain cases the phenol may be formed by acyl migration (21).

A similar reaction occurs in the irradiation of an α-pyrone (XXXI). Irradiation of this in methanolic solution gives, again presumably through the ketene, the corresponding ester; the stereochemistry of the product is unknown (103).



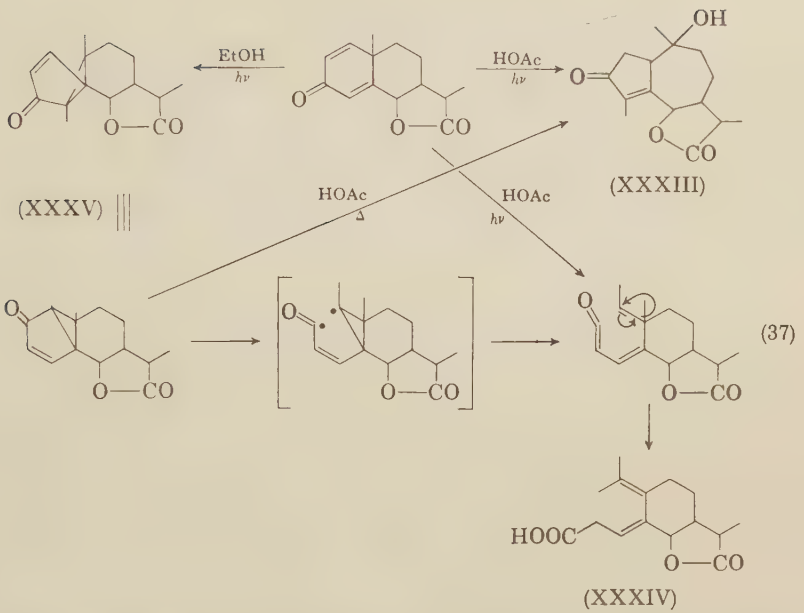
(XXXI) (36)

The mode of genesis of the above substances offers no difficulties, in outline at least, and the first step is similar to that initiating the vitamin D transformations (page 404) wherein X and Y are quaternary carbon atoms. A substance for which the structure XXXII has been proposed has been isolated in very small yield by the irradiation of β-ionone.



(XXXII)

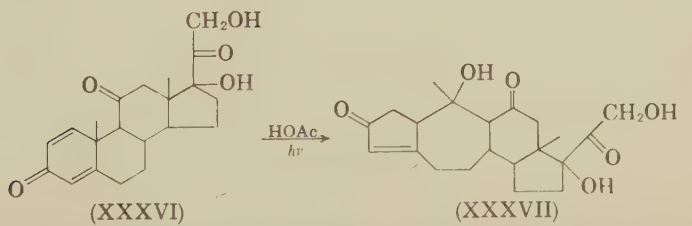
Cross-conjugated homoannular dienones also undergo a number of interesting transformations. This study, one of the earliest in photochemistry, derives from the researches of Canizzaro, Francesconi, and their colleagues at the turn of the century, on the chemistry of santonin (240). Among the products found, under the various conditions of irradiation used, were isophotosantonic acid (now isophotosantonic lactone), photosantonic acid (and the related ethyl ester photosantonin), and certain other dimeric substances the structures of which have not been elucidated as yet. Isophotosantonic lactone has recently been shown to be XXXIII (13,18,273), and this transformation makes available a new route into the perhydroazulene series, and so to the guaianolide and other sesquiterpenoids. Equivalent transformations have also been carried out in stereoisomers of santonin and on artemesin (19). The production of isophotosantonic lactone by irradiation of santonin in aqueous acetic acid solution leads also to the formation of photosantonic acid (XXXIV) (273). The use of other solvents, e.g., ethanol, permits isolation of an intermediate between santonin and photosantonic acid. This substance, lumisantonin, is also produced (as the corresponding hydroxy acid) by irradi-



(37)

ation of santonin in one equivalent of aqueous potassium hydroxide (80). Lumisantonin has been shown to be XXXV (3,15), and on irradiation in acetic acid it is transformed into photosantonic acid. Remarkably, on heating in aqueous acetic acid it is transformed into isophotosantonic lactone.

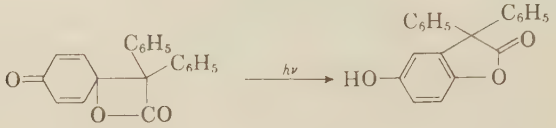
The conversion of lumisantonin to photosantonic acid probably proceeds through the ketene-carbene (299) as indicated.* An analogous transformation to that involved in the formation of XXXIII has been carried out in the steroid series on prednisone acetate (XXXVI) (17) to give XXXVII.



(38)

* Other processes involving cyclopropane ring cleavage and methyl radical migration to a dienone may be envisaged and obviate the necessity of carbene formation. The irradiation of umbellulone itself in the absence of a solvent leads to the formation of thymol in quantitative yield (285).

These reactions by no means delineate all the range of transformations undergone by cross-conjugated dienones. As early as 1911 it was observed by Staudinger that the β-lactone (XXXVIII) on irradiation

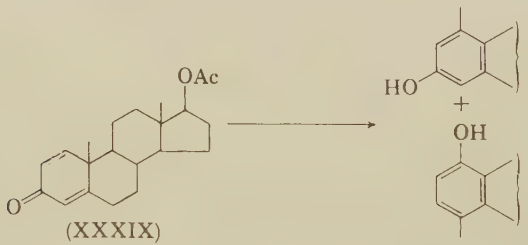


(XXXVIII) (39)

in benzene underwent the equivalent of a dienone-phenol rearrangement (245). The conversion of XXXVIIIa to XXXVIIIb, however, has been shown to be a free radical chain reaction presumably initiated by homolytic cleavage to the dichloromethyl radical (317).

(XXXVIIIa) (XXXVIIIb)

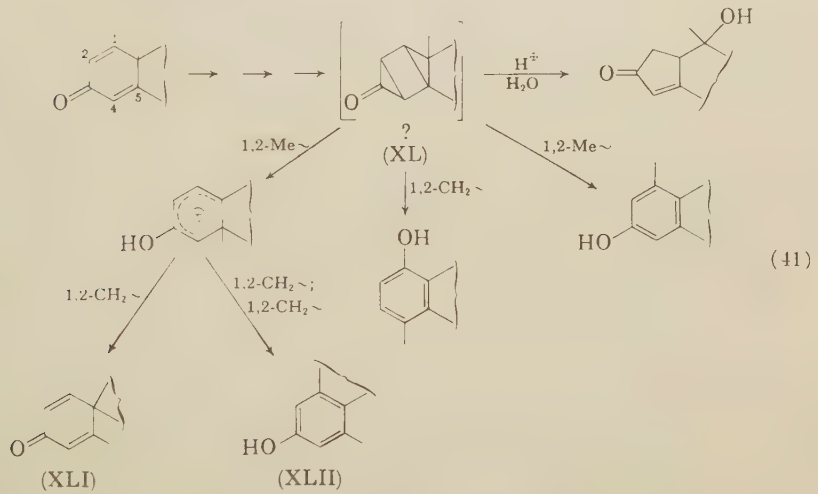
Recently it has been shown that prolonged irradiation of the dienone (XXXIX) gave a large number of products, some of which were neutral and some phenolic (100). Two of the phenolic products were identified as those produced by the two types of dienone-phenol rearrangement, wherein methyl or methylene migrates (291). These products are of considerable interest, since their formation in a non-acidic medium would imply some mode of genesis other than the normal. It is conceivable that both these products, as well as those



(XXXIX) (40)

of the perhydroazulene class, may arise from the same type of intermediate. This may be formally represented as XL, or an excited equivalent approaching thereto, which might be expected to accept

even water as acid and base.* If correct, then other rearrangement products, such as those of the Westphalen type, would be expected. Very recently (272) the structures of additional transformation products have been elucidated, two of which, XLI and XLII, involve just such a change. When a methyl group at C-4 is introduced, however, a substance of the lumisantonin type is the main product. The manner in which the methyl group at C-4 exerts so considerable an effect is not yet clear, unless it is the mere stabilization of an intermediate radical.



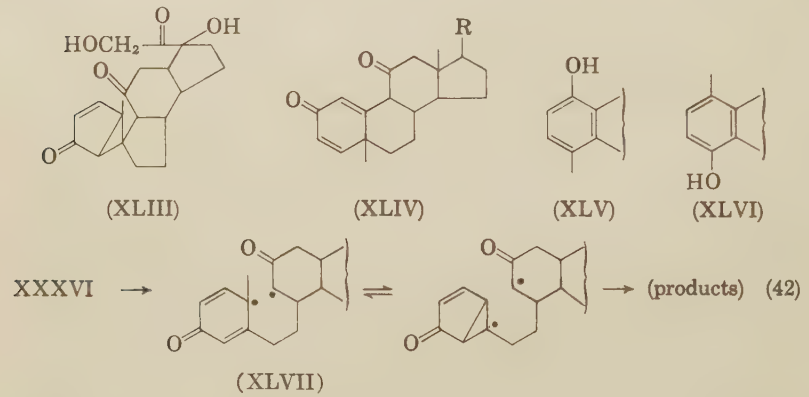
(41)

The solvent plays an important but secondary part in these transformations. Its nature, quite apart from its purely physical properties such as optical transparency, will be of great importance with regard to the product actually isolated. Many of these initial photoisomerization products may be reversibly formed, either thermally or photochemically. The presence of acids (either added or produced in traces by oxidation) may catalyze the decomposition of an intermediate and so appear to catalyze the over-all reaction either at the expense of some other reaction or when no other reaction appears to occur. Thus, while supposed photo-reactions may in fact be acid-

* It should be noted that whatever the nature of the intermediate, here represented by XL, no evidence yet exists for the intermediacy of a C-2 to C-4 bond as far as products are concerned.

induced, the light being irrelevant, it can also be that both light *and* other reagents may be necessary for over-all reaction.

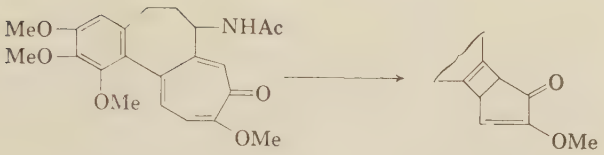
The presence of other functional groups may modify a reaction. Although irradiation of prednisone acetate (XXXVI) in acetic acid gives the perhydroazulene derivative, as in the case of santonin, irradiation in ethanol does not, apparently, lead to products corresponding to photosantonin. Instead, lumiprednisone acetate (XLIII) is formed, together with neoprednisone acetate (XLIV) and a phenol (XLV or XLVI). It has been suggested (17) that the presence of the carbonyl group weakens the C-9 to C-10 bond, facilitating the formation of the biradical (XLVII). This could lead, simply, to lumiprednisone, from which, by the migration of suitable bonds, the other products may be derived (equation 42); it has in fact been shown that



irradiation of lumiprednisone acetate itself can lead to the phenol. However, since the formation of neoprednisone acetate from lumiprednisone acetate would equally suggest the reversibility of the formation of lumiprednisone from prednisone, then the phenol may equally be formed through an intermediate of type XL, as may, in fact, neoprednisone itself.

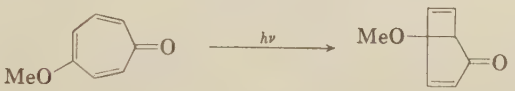
VII. Tropolones

The tropolone ring may be thought of, formally, as containing the trienone system. The first substance in which light-induced transformations were reported was the alkaloid colchicine (XLVIII), from which three lumicolchicines have been prepared. It is interesting that two of these have been found in nature (211).



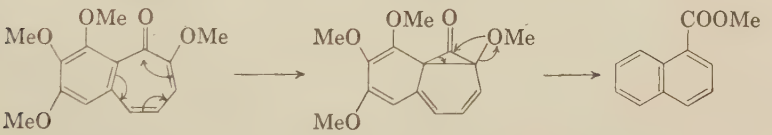
(XLVIII) (XLIX) (43)

It seems probable that the β-isomer is represented by XLIX, although direct evidence of the size of ring B is lacking (108,112). The γ-isomer is believed to be a stereoisomer. γ-Tropolone has been reported to give a product on irradiation (equation 44) (61) which is formed by an entirely analogous rearrangement.



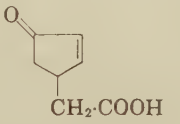
(44)

The rearrangement of tetramethylpurpurogallin (XLIXa) gives the naphthoic ester (XLIXb) by an intramolecular rearrangement (306). A possible course is that indicated. The irradiation of α-



(XLIXa) (XLIXb)

tropolone itself gives XLIXc (307). The mechanism of this conversion is unknown, but an intermediate of the bicyclo[3.2.0]heptadiene type (as found in colchicine and γ-tropolone) has been proposed.



(XLIXc)

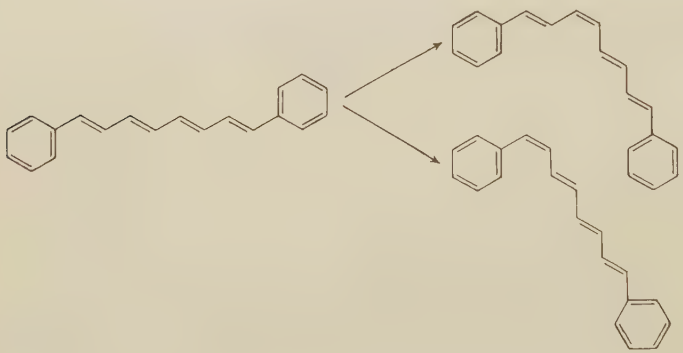
VIII. Ethylenic Systems

A. ISOMERIZATION

One of the best known and possibly the most used of photochemical transformations is that of isomerization about a double bond. As an example, the conversion of fumaric acid to the *less stable* maleic acid

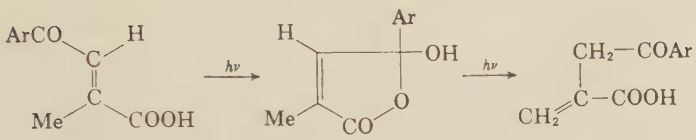
may be quoted, and it appears to be the general rule that irradiation favors the less stable isomer in what appears to be a photoequilibrium (208, 319). The detailed mechanism of the light-induced transformation is not clearly established (113) and may, indeed, be different depending on the absorbing system (157,185,186,203,292).

The equilibrium in the maleic–fumaric acid system contains about 75% maleic (*cis*) and 25% fumaric (*trans*) acids (185). Similar isomerizations have been found for cinnamic acid (in solution) and substituted cinnamic acids (249,250), tiglic acid (195), stilbene (157), dichloroethylene (161,187), indigo (43), thioindigo (44), and several other substances including dyestuffs (177,252,252a,253). The technique has been used in the field of extended polyenes (297,298), and as examples may be quoted the preparation of 1- and 3-mono-*cis*-diphenyloctatetraene from the all-*trans* isomer (equation 45) and the con-

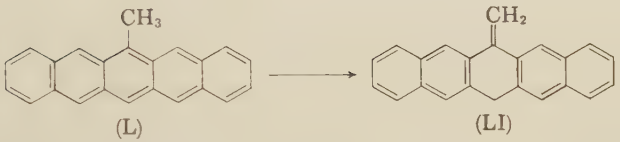


(45)

version of *cis*-β-carotene to all-*trans* β-carotene (130,131). Such isomerizations are to be regarded as unexceptional, and the literature is large (292). The transformation is not restricted, apparently, to isolated or conjugated double bonds, for a similar isomerism has been recorded for the cumulene diphenylbutatriene (116). Such isomerizations are occasionally accompanied by more profound transformations. Thus, certain aroyl acrylic acids on irradiation are indeed isomerized to the *cis* isomer, but a further step is then said to occur (160) with the formation of a vinyl group. This latter transformation (equation 46) is very unusual; a related isomerization is the conversion of L to LI (79).

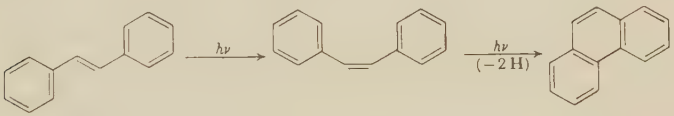


(46)



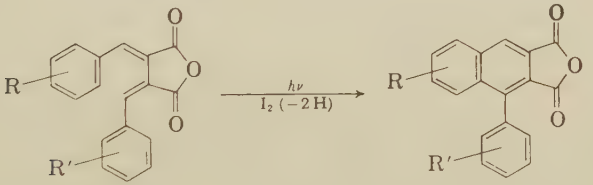
(47)

Stilbene may be isomerized to *cis*-stilbene, but in dilute solution is further transformed into phenanthrene (equation 48) (54,190). The nature of the hydrogen transfer step is not known. In more



(48)

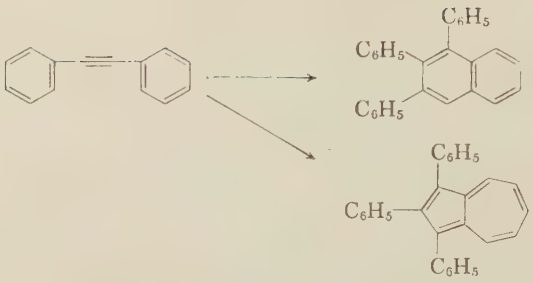
concentrated solution tetraphenylcyclobutane is formed by dimerization (66,111,189). A somewhat related transformation is the cyclization of certain dibenzalsuccinic anhydrides (equation 49) (7,246),



(49)

but in these reactions a trace of iodine is necessary. Furthermore an analogous dark reaction can be performed at high temperatures.

It may be mentioned here that little work has been reported on the irradiation of acetylenic compounds, apart from acetylene itself. That synthetic possibilities lie in this direction is shown by the formation of an azulenic and a naphthalenic dimer by the irradiation of diphenylacetylene (equation 50) (52).



(50)

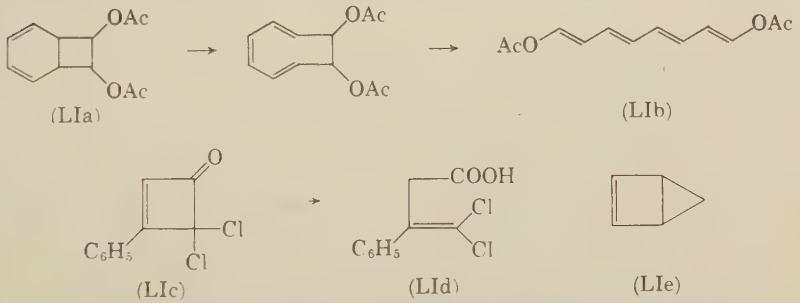
Cis-trans interconversions about carbon-nitrogen double bonds have not been so much studied as have the ethylenic equivalents. In some cases, such as benzalaniline, no geometrical isomerism has been detected, and this appears to be generally true for aromatic compounds (287); in fact, it has been doubted whether such compounds may exist in two forms. In work at very low temperatures, however, changes have been observed which have been attributed to such isomerism (107). The problem of such isomerism as it affects dyestuffs and related substances has been considered (45) in connection with generally observed phototropic changes, and the conclusion has been reached that *cis-trans* isomerism accounts for but a part of such phenomena (278). Light-induced isomerism about the carbon-nitrogen double bond has been recorded in the irradiation of cinnamaldehyde azine (cinnamalazine) (89,159), and it is known in certain oximes and their *o*-ethers (39,67,77,251).

The isomerism of compounds containing the nitrogen-nitrogen double bond is well established. It was first noted by Hartley in 1937, when he obtained *cis*-azobenzene by irradiation and fractional crystallization of the *trans* isomer (120). The technique of chromotography has since been applied to this and other azo compounds with success. Among the isomers prepared are *cis*-2,2′-azonaphthalene and *cis*-2,2′-azopyridine (59,109,296). With substituted azo and with bis- and polyazo, compounds the situation is more complex, but the phenomenon appears well established (314). The reversion of the *cis* compounds to the *trans* takes place in the dark, particularly at elevated temperature, and in ortho-substituted azo compounds is especially facile. Similar reports have been made about aryl diazosulfonates (139).

B. CONJUGATED ETHYLENIC SYSTEMS

Apart from the occurrence of geometrical isomerism little information has been recorded as to the results of the irradiation of dienes, trienes, etc. One general observation of importance, exposition of which falls outside the scope of this article, is that homoannular dienes, in the presence of a sensitizer, readily add oxygen to give cyclic peroxides in the manner of a Diels-Alder reaction (see, for instance, 326). Another reaction, again involving oxygen but with alkenes, is the formation of allylic hydroperoxides (27,104,212,327).

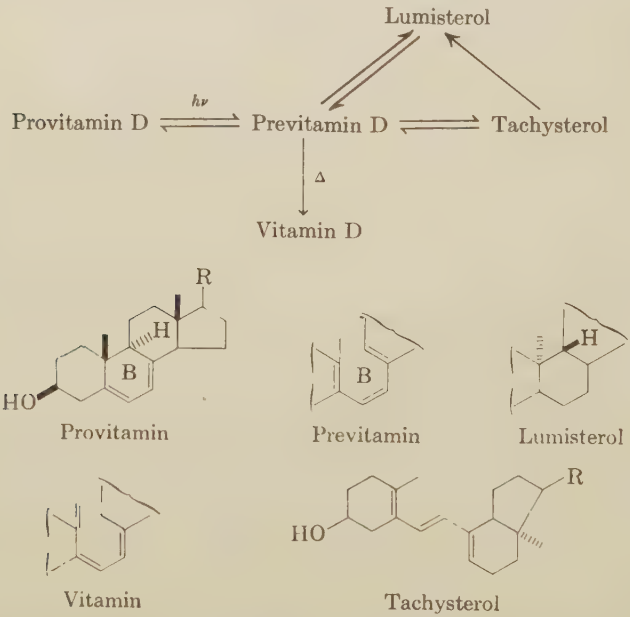
The irradiation of cyclohexadiene in the absence of oxygen has been shown, as expected in view of the systems already referred to, to give hexa-1,3,5-triene (21,329). Of more interest, and illustrative of the probable generality of the reaction, are the conversions of LIa to LIb and LIc to LId (21). In cyclic systems with odd numbers of carbon



atoms, bridging may be expected (compare, for instance, certain of the tropolones). However, cyclopentadiene is reported as not giving bicyclopentene (LIe) because of rapid dimerization of the starting material (21).

One of the few transformations of homoannular dienes is of particular interest and importance: the formation of calciferol. The mode of conversion of ergosterol and 7-dehydrocholesterol into vitamins of the D group and the structures of the several related products have been a subject of study for many years. The researches have resulted in a voluminous proliferation of papers which in its mere bulk reflects the difficulties inherent in the problem—a problem which has by no means been resolved. It is possible here only to summarize the results which have a particular photochemical interest (31,40,106,156,276, 279,280,284).

Until recently attention was directed for the main part to the structures of the various substances formed on irradiation of the provitamin, and this phase is now closing.* The problem of the order and mode of formation is at once more complex and more subtle, since several equilibria appear to be involved. The scheme depicted in equation 51 represents what is probably an approximation to the truth, though recent work has suggested that more than one activated intermediate may be involved (200,201). The remaining problem concerns the immediate origin of tachysterol and lumisterol. It may also be noted that the ergosterol-precalciferol change falls into the general category already discussed (page 393). A number of other isomers of these substances are known (132,133,329).



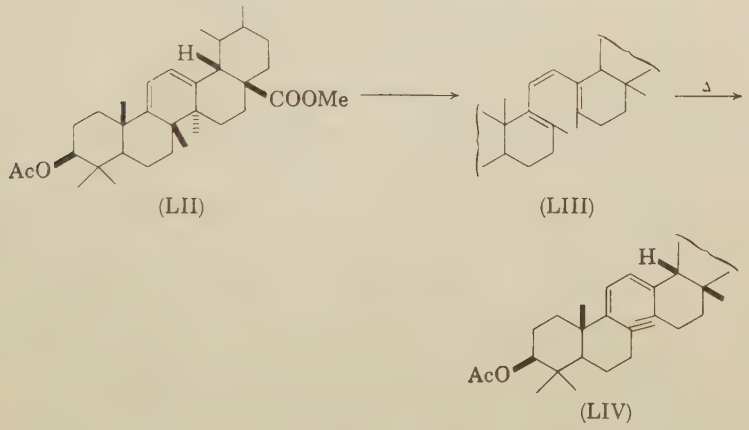
The transformation to calciferol involves the cleavage of a diallyl bond and, directly or indirectly, the rearrangement of a triene. The

* This may well be a rash statement, since about 1948–49 it was believed that the structures and relationships of the entire series had been established. As a result of the work of Velluz and his associates and the isolation of previtamin D, the field was a subject of renewed interest. As a consequence, the configurations of tachysterol and lumisterol were revised (60,274,275).

nature of the intermediate(s) is not yet clear (121). A related intermediate has been assumed to play a part in the transformation of dehydroergosterol (see page 406).

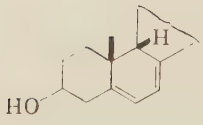
The irradiation of 19-nor-$\Delta^{5,7}$-androstadiene-3β,17β-diol and of 7-dehydro-19-norcholesterol has recently been shown to give derivatives of 19-nortachysterol (277).

Very recently a transformation entirely analogous to that leading to the formation of precalciferol has been reported in the triterpenoid series (4). The irradiation of methyldehydroursolate acetate (LII) gives LIII, the latter being transformed by heat to LIV. Analogous changes are said to occur in other triterpenoids containing the same chromophore in the same stereochemical environment, and further transformation products of unknown constitution, which must now, however, be expected to be related to the corresponding ergosterol derivatives, have been reported (135).

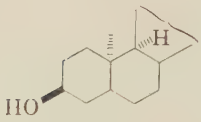


(LII) (LIII) (LIV) (52)

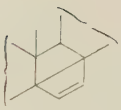
The requirements for these transformations are not, however, merely the presence of a homoannular diene. Thus, the action of heat on calciferol leads to the formation of two isomeric products, pyrocalciferol (LV) and isopyrocalciferol (LVI). Irradiation of isopyrocalciferol and of pyrocalciferol, which possess the C_9–C_{10} *syn* structures, leads to carbon-carbon bond *formation*, not cleavage, the resultant products being considered to contain the part structure of type LVII (90). Such a transformation is formally analogous to



(LVI)

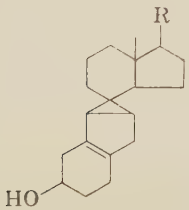


(LV)

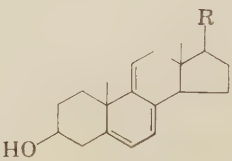


(LVII)

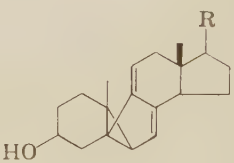
that observed in the tropolones. Further irradiation of calciferol leads to Suprasterol-II, for which structure LVIII has recently been proposed (91).



(LVIII)



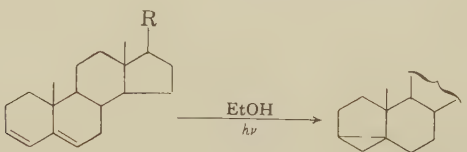
(LIX)



(LX)

Dehydroergosterol (LIX) containing an extra conjugated double bond has also been irradiated (289). The structure of the photoproduct has recently been investigated and shown to be LX (16). In this case, also, the C-9 to C-10 bond is involved: the reaction has been shown to retain the steric integrity of the C-10 methyl group (22).

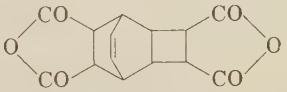
The only case so far reported of the transformation product derived from a purely heteroannular diene is that from 3,5-cholestadiene (LXa). The pentacyclic LXb is obtained (310), the cyclopropane ring being of *opposite* configuration from the 3,5-cyclosteroids obtained from the solvolysis of cholesteryl ester.



(LXa) (LXb)

C. AROMATIC SYSTEMS

Benzene and its homologues have been believed, until recently, to be stable to photochemical excitation. The difficulty in observing products would, in part, be due to the fact that any intermediate formed would revert to the stable aromatic system unless trapped. Recently maleic anhydride has been used as such a trap (304) and the product isolated for which the structure LXc has been proposed. It would be formed by 1,2 addition followed by a normal Diels-Alder reaction.



(LXc)

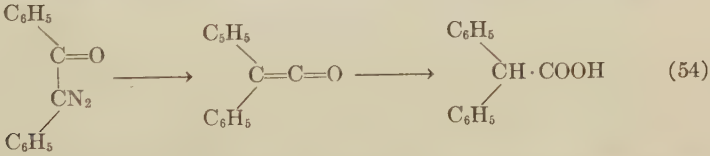
The irradiation of benzene itself has been reported to give small amounts of fulvene (305).

IX. Diazoketones

The diazoketones are susceptible to light-induced activation, and the products obtained may be interpreted (though not necessarily) as derived from so-formed carbenes. Rearrangements (equations 53

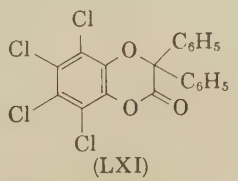
$$—CO—CN_2— \longrightarrow —CO—\bar{C}— \longrightarrow \text{(products)} \qquad (53)$$

and 54) analogous to the Arndt-Eistert are, therefore, recorded (124,125,257,286,322). But the intermediate ketene may also be



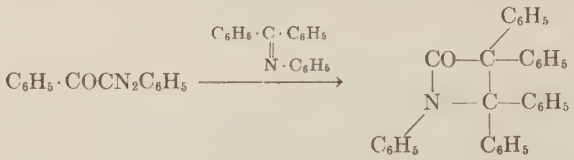
(54)

trapped, and in the above case irradiation in ether containing tetrachloro-*o*-quinone gives a lactone, LXI (124). This type of reaction



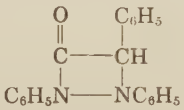
(LXI)

has recently been extensively investigated with the discovery of a number of particularly interesting transformations. Among these may be cited the formation of propiolactams (equation 55) (147), the

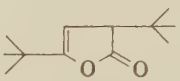


(55)

reaction of α-diazodeoxybenzoin with azobenzene to give LXII (124), and the photolysis of diazomethyl-*tert*-butyl ketone in the absence of solvent to give LXIII (286). This last reaction, however, appears not to be general. An important reaction which does appear to be general is the photolysis of *o*-quinonediazide and related substances to give ring-contracted products (137,256,321). Some of these are illustrated in Table IV.



(LXII)

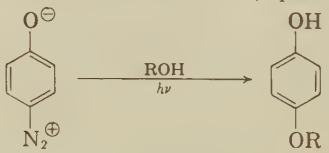


(LXIII)

In contrast to the above, diazoesters, on decomposition, undergo addition reactions with unsaturated systems to give cyclopropane rings and further transformation products of these (214). Similar reactions are, of course, well known, following thermal decomposition of the diazoester. It has been claimed, however, that photochemical decomposition leads, in the case of reaction with benzene, to norcaradiene derivatives, whereas with thermal decomposition rearrangement to the cycloheptatriene form takes place (equation 56) (see, however, 328).

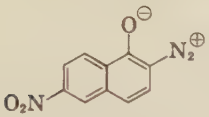
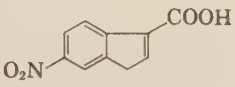
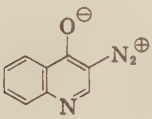
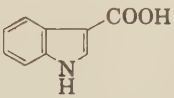
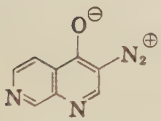
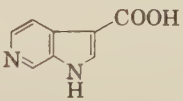
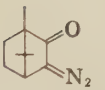
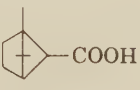
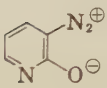
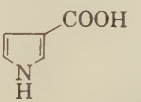
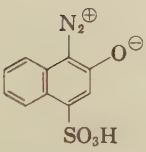
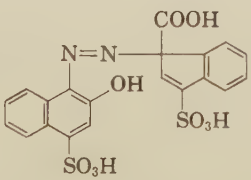
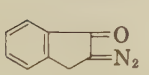
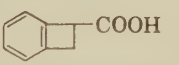
(56)

A number of reactions related to those of the *o*-quinonediazides take place with *p*-quinone derivatives (equation 57) and with their



(57)

TABLE IV

Substance	Product	Ref.
		259
		260
		262
		127
		262
		257
		60a

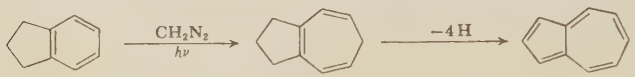
related compounds (equation 58) (261). A number of associated

(58)

reactions have been reported in the decomposition of acid azides (124,242).

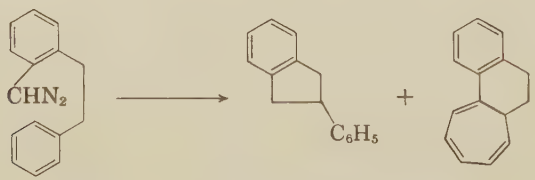
X. Diazoalkanes

Simple aliphatic azo compounds absorb in the 340 mμ region. Decomposition in the gas phase leads to the formation of nitrogen and hydrocarbons, but in solution carbenes are formed which attack the solvent. An important application of this has been the decomposition of diazomethane in benzene solution to give seven-membered rings (1,94,97,98,269). This technique has been used for the synthesis of tropones, azulenes, terpenes, and related substances, as, for instance in the synthesis of azulene according to equation 59. Recently



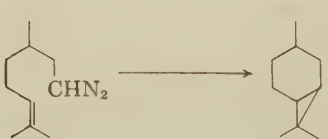
(59)

the claim has been made that the initial product in the reaction of benzene with methylene is in fact a mixture of cycloheptatriene and norcaradiene, the latter being converted in practically quantitative yield to the former by heating (168). Confirmation of this would be desirable. The reaction is not, of course, limited to diazomethane; however, few other applications seem to have been made, although the method would appear to have a wide scope. Among those in which an intermediate diazoalkene is decomposed photolytically may be mentioned that of a phenyldiazomethane (equation 60) (119) and

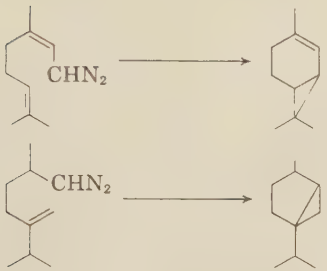


(60)

syntheses of carane, carene, and thujane (equations 61–63) (52). In



(61)



(62)

(63)

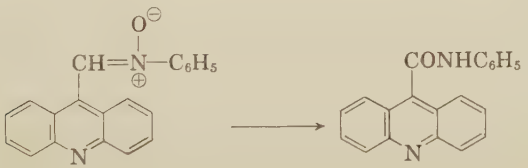
the last case the reaction is not apparently stereospecific, there being two diastereoisomers produced. Again, in these reactions, the carbene is probably, but not necessarily, involved.

XI. Oxygen Transfer Reactions

This group comprises several potentially useful transformations which have not yet been exploited to any great extent.

A. NITRONE–AMIDE REARRANGEMENT

This may be exemplified by the conversion of 9-acridyl-*N*-phenylnitrone into the anilide (equation 64) (62,162). A similar, and un-

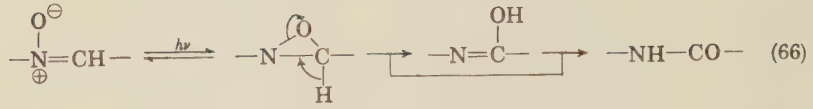


(64)

doubtedly related, transformation is involved also in the conversion of quinoxaline *N*-oxide to 2-hydroxyquinoxaline (equation 65) (154).

(65)

The intermediate in these transformations is presumably the three-membered heterocycle, and the formation of such substances has recently been observed in the irradiation of nitrones (equation 66)



(66)

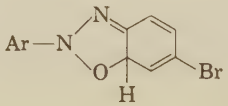
(140,152). The reaction may be reversible in the dark with re-formation of the nitrone. The oxazirane nature of the intermediate has been established in one case by direct comparison with the product obtained by the peracid oxidation of the related Schiff base (244). In some cases, e.g., α-(*p*-nitrophenyl)-*N*-phenylnitrone, the irradiation product is rapidly converted to the anilide, and an identical result was obtained with the oxazirane prepared by oxidation of the Schiff base (102,128).

B. AZOXYBENZENE–*o*-HYDROXYAZOBENZENE REARRANGEMENT

The light-induced rearrangement of azoxybenzene (88) has been reinvestigated recently (8). It has been found that the oxygen is transposed into the aromatic ring *not* adjacent to the nitrogen-bearing oxygen (equation 67). It will be noted that, formally, this is an

(67)

addition vinylogously related to the nitrone-amide transformation which in simple terms would suggest an intermediate such as:



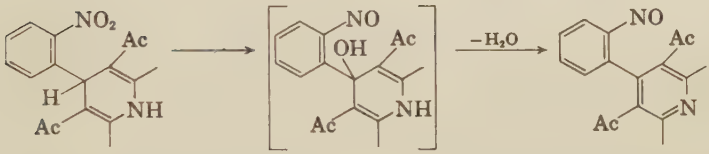
C. *o*-NITROBENZALDEHYDE–*o*-NITROSOBENZOIC ACID REARRANGEMENT

It was first observed by Ciamician and Silber (65) that irradiation of *o*-nitrobenzaldehyde led to the formation of *o*-nitrosobenzoic acid. The same reaction did not, however, occur with the *m*- or *p*-isomers. The *o*-reaction has some generality as may be seen in the examples shown in equations 68–71 (29,209,238,256,263).

(68)

(69)

(70)



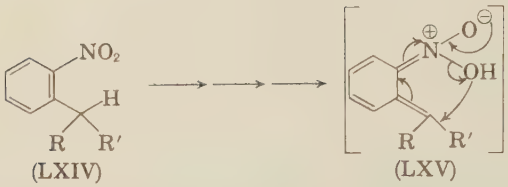
(71)

From the mechanistic point of view it is interesting that irradiation in alcoholic solution of the *o*-nitroaldehyde gives the corresponding ester, and a modification which may have potentialities as a protecting group lies in the fact that the acetals of the aldehydes are converted into the half-esters, thus releasing one of the alcohol hydroxyl functions at a time (equation 72) (9,265). There have been a number of

(72)

studies aimed at the elucidation of the mechanism of the *o*-nitrobenzaldehyde rearrangement (153,155,263). It is apparently intramolecular with a quantum efficiency of 0.5 and—a fact of importance—can occur in the solid. It resembles, formally, the numerous base-catalyzed oxidation-reduction processes common in *o*-nitro compounds, the mechanism of which also does not appear to have been established (cf., for instance, 218).

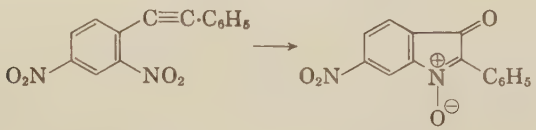
The general process in all cases appears to require the part structure LXIV. Conceivably the initial step might be removal of the benzylic



(73)

hydrogen atom by the activated nitro group. Electronic redistribution could then give an intermediate such as LXV wherein addition of oxygen to the benzylic position is now feasible. However, it is presumably not necessary that a discrete intermediate in the ground state should be involved.*

Related transformations include the formation of isatogens (and derivatives) from *o*-nitrotolanes and from *o*-nitrostilbene, *o*-nitrocinnamic acid, *o*-nitrostilbene chloride, and other substances (96, 151,196,197,204,243,254,264).



(74)

XII. Miscellaneous Reactions

In addition to the foregoing specifically light-catalyzed transformations light has been claimed to effect a wide range of chemical transformations. Among these may be mentioned chromate oxidation (38,309), the Canizzaro reaction (144), and the dehydrogenation of quinones (42,78,95,101,129,226) and of other substances in the presence (58,283) and in the absence (99,169,188,288) of quinones.

Polymerizations may be induced by light in at least two ways. Photolysis may give rise to free radical initiators, or the photoactivated species itself may be the initiator (11,150,170,268). As far as the analysis of products would indicate, there is, apparently, a close relationship between the free radical and light-induced polymerizations (23,55).

* Leighton and Lucy considered that vibrational energy brought the oxygen atom sufficiently close to the benzylic hydrogen (in the case of the aldehyde) for redistribution of electrons to give the product with migration and interposition of the oxygen atom in a continuous process (155).

The decomposition of diazonium salts in water and in the halogen acids may be induced by light to give good yields of the phenols and aryl halides (258). In alcohol at 0° both reduction and substitution take place (126,138). A reaction in overall approximate to the Claisen rearrangement has been reported (145), while there are numerous references to the addition of water (171,252,255,281) and of alcohols (270,271) to unsaturated systems. Photolytically generated phenyl radicals have been used for phenylation (302). Nitrosyl chloride has been used for nitration of hydrocarbons to give oximes (323).

XIII. Experimental

A. IRRADIATION OF 6-METHYL-6-ACETOXYCYCLOHEXA-2,4-DIENONE (20)

6-Methyl-6-acetoxycyclohexa-2,4-dienone (1.53 g.) in ether (1.5 liters) saturated with water was irradiated in a pyrex flask under reflux with a bare mercury arc (500 watts) lamp until the ultraviolet absorption at 299 mμ had disappeared completely (2 hours). Removal of the solvent from the dried ($MgSO_4$) solution afforded an oily product which solidified on cooling to give 6-acetoxy-3,6-heptadienoic acid, m.p. (from cyclohexane) 86–87° (1.09 g.).

B. PREPARATION OF Δ^2-CYCLOHEXENYLDIMETHYLCARBINOL (166)

A solution of pure, dry acetone (59 g.) in pure, dry, peroxide-free cyclohexene (275 ml.) was placed in a quartz irradiation apparatus (page 370) and irradiated by a 125 watt mercury vapor lamp at 15 - 20° (water cooling), with exclusion of oxygen and water, for 100 hours, when the ketone band has disappeared from the infrared spectrum of the solution.

The solvent was removed at atmospheric pressure, and the residue, a viscous yellow oil (100 g.), distilled under reduced pressure; the fraction (70 g.) distilling between 80 and 180° at 40 mm. was collected.

The distillate was separated by vapor phase chromatography over a silicone column into two constituents. The lower-boiling fraction (36.5 g.) had b.p. 82°/30 mm., n_D^{21} 1.4740, and was pure cyclohexenyldimethylcarbinol.

C. PREPARATION OF 2,6-DIMETHYL-4-PYRONE DIMER (294)

The dimethylpyrone was spread out in a thin layer on aluminum foil (65 g. on a 2 × 2 foot area) and irradiated with a General Electric sun lamp placed about 2 feet above the foil (if the lamp is placed closer, much of the pyrone is lost by sublimation). The pyrone was irradiated for 14 days, during which time it was frequently raked to expose new surfaces. The product was extracted with two 200 ml. portions of boiling acetone to remove unreacted monomer, and the residual dimer was crystallized from dimethylformamide (ca. 65 ml. of solvent per g. of dimer) to give white needles, m.p. 281–284° dec. (sealed capillary). The yield was ca. 30%.

References

1. Alder, K., and P. Schmitz, *Chem. Ber.*, *86*, 1539 (1953).
2. Applequist, D. E., R. L. Litle, E. C. Friedrich, and R. E. Wall, *J. Am. Chem. Soc.*, *81*, 452 (1959); Applequist, D. E., E. C. Friedrich, and M. T. Rogers, *J. Am. Chem. Soc.*, *81*, 457 (1959).
3. Arigoni, D., H. Bosshard, H. Bruderer, G. Büchi, O. Jeger, and L. J. Krebaum, *Helv. Chim. Acta*, *40*, 1732 (1957).
4. Autrey, R. L., D. H. R. Barton, and W. H. Reusch, *Proc. Chem. Soc.* (*London*), *1959*, 55.
5. Bachmann, W. E., *J. Am. Chem. Soc.*, *55*, 391 (1933).
6. Bachmann, W. E., in A. H. Blatt, *Organic Syntheses*, Coll. Vol. II, Wiley, New York, 1943, p. 71.
7. Baddar, F. G., L. S. El-Assal, and M. Gindy, *J. Chem. Soc.* (*London*), *1948*, 1270.
8. Badger, G. M., and R. G. Buttery, *J. Chem. Soc.* (*London*), *1954*, 2243.
9. Bamberger, E., and F. Elgar, *Ann.*, *371*, 319 (1910); *475*, 288 (1929).
10. Bamford, C. H., and R. G. W. Norrish, *J. Chem. Soc.* (*London*), *1938*, 1521.
11. Bamford, C. H., and M. J. S. Dewar, *Nature*, *163*, 214 (1949).
12. Barnard, M., and N. C. Yang, *Proc. Chem. Soc.* (*London*), *1958*, 302.
13. Barton, D. H. R., P. de Mayo, and M. Shafiq, *J. Chem. Soc.* (*London*), *1957*, 929.
14. Barton, D. H. R., A. da S. Campos-Neves, and A. I. Scott, *J. Chem. Soc.* (*London*), *1957*, 2698.
15. Barton, D. H. R., P. de Mayo, and M. Shafiq, *J. Chem. Soc.* (*London*), *1958*, 140.
16. Barton, D. H. R., and A. S. Kende, *J. Chem. Soc.* (*London*), *1958*, 688.
17. Barton, D. H. R., and W. C. Taylor, *J. Chem. Soc.* (*London*), *1958*, 2500.
18. Barton, D. H. R., P. de Mayo, and M. Shafiq, *J. Chem. Soc.* (*London*), *1958*, 3314.
19. Barton, D. H. R., and J. E. D. Levisalles, cited by Barton, D. H. R., *Proc. Chem. Soc.* (*London*), *1958*, 65.

20. Barton, D. H. R., and G. Quinkert, *Proc. Chem. Soc. (London), 1958,* 197.
21. Barton, D. H. R., *Helv. Chim. Acta, 42,* 2604 (1959).
22. Barton, D. H. R., R. Bernasconi, and J. Klein, *J. Chem. Soc. (London), 1960,* 511.
23. Bawn, C. E. H., *The Chemistry of High Polymers,* Interscience, New York, 1948, pp. 13–18.
24. Benson, S. W., and G. B. Kistiakowsky, *J. Am. Chem. Soc., 64,* 80 (1942).
25. Bergmann, E., and S. Fujisi, *Ann., 483,* 65 (1930).
26. Bergmann, F., and Y. Hirshberg, *J. Am. Chem. Soc., 65,* 1429 (1943).
27. Bergmann, W., and M. J. McLean, *Chem. Revs., 28,* 367 (1941).
28. Bernstein, H. J., and W. C. Quimby, *J. Am. Chem. Soc., 65,* 1845 (1943).
29. Berson, J. A., and E. Brown, *J. Am. Chem. Soc., 77,* 447 (1955).
30. Billeter, J. R., and K. Miescher, *Helv. Chim. Acta, 34,* 2053 (1951).
31. Bills, C. E., in W. H. Sebrell and R. S. Harris, *The Vitamins,* Vol. II, Academic Press, New York, 1954, pp. 132 *ff.*
32. Blacet, F. E., and J. G. Calvert, *J. Am. Chem. Soc., 73,* 661, 667 (1951); Blacet, F. E., and J. D. Heldman, *J. Am. Chem. Soc., 64,* 889 (1942); Blacet, F. E., and J. N. Pitts, *J. Am. Chem. Soc., 74,* 3382 (1952); and other papers in this series.
33. Blacet, F. E., and A. Miller, *J. Am. Chem. Soc., 79,* 4327 (1957).
34. Bogert, M. T., and T. Hasselstrom, *J. Am. Chem. Soc., 52,* 4093 (1930).
35. Bots, J. P. L., *Rec. trav. chim., 77,* 1010 (1958).
36. Bowen, E. J., and A. T. Horton, *J. Chem. Soc. (London), 1936,* 1685.
37. Bowen, E. J., *Chemical Aspects of Light,* Oxford Univ. Press, London, 1946.
38. Bowen, E. J., and E. T. Yarnold, *J. Chem. Soc. (London), 1929,* 1648; Bowen, E. J., *Nature, 177,* 889 (1956).
39. Brady, O. L., and F. P. Dunn, *J. Chem. Soc. (London), 103,* 1619 (1913); Brady, O. L., and G. P. McHugh, *J. Chem. Soc. (London), 125,* 549 (1924).
40. Braude, E. A., and O. H. Wheeler, *J. Chem. Soc. (London), 1955,* 320.
41. Bridge, N. K., and G. Porter, *Proc. Roy. Soc., A244,* 259 (1958), and other papers in this series.
42. Brockmann, H., and R. Muhlmann, *Ber., 82,* 348 (1949).
43. Brode, W. R., and G. M. Wyman, *J. Am. Chem. Soc., 73,* 4267 (1951).
44. Brode, W. R., and E. G. Pearson, and G. M. Wyman, *J. Am. Chem. Soc., 76,* 1034 (1954).
45. Brode, W. R., in *Roger Adams Symposium,* Wiley, New York, 1955, p. 8.
46. Brunet, V., and W. A. Noyes, *Bull. soc. chim. France, 1958,* 21.
47. Büchi, G., C. G. Inman, and E. S. Lipinsky, *J. Am. Chem. Soc., 76,* 4327 (1954).
48. Büchi, G., and N. C. Yang, *Helv. Chim. Acta, 38,* 1338 (1955); *J. Am. Chem. Soc., 79,* 2318 (1957).
49. Büchi, G., J. T. Kofron, E. Koller, and D. Rosenthal, *J. Am. Chem. Soc., 78,* 876 (1956).
50. Büchi, G., and I. M. Goldman, *J. Am. Chem. Soc., 79,* 4741 (1957).
51a. Büchi, G., T. Curphey, J. Kauffmann, and P. de Mayo, unpublished observations.
51b. Biemann, K., private communication, 1959.
52. Büchi, G., private communication, 1959.

53. Buchschacher, P., J. Kalvoda, D. Arigoni, and O. Jeger, *J. Am. Chem. Soc., 80*, 2905 (1958).
54. Buckles, R. E., *J. Am. Chem. Soc., 77*, 1040 (1955).
55. Burnett, G. M., *Quart. Revs. (London), 4*, 292 (1950).
56. Butenandt, A., A. Wolff, and P. Karlsoi, *Ber., 74*, 1308 (1941); Butenandt, A., W. Friedrich, and L. Poschmann, *Ber., 75*, 1931 (1942); Butenandt, A., and L. Poschmann, *Ber., 77*, 392, 394 (1944).
57. Butenandt, A., L. Poschmann, G. Failer, U. Schiedt, and E. Biekert, *Ann., 575*, 123 (1951).
58. Calvin, M., and G. D. Dorough, *J. Am. Chem. Soc., 70*, 699 (1948).
59. Campbell, N., A. W. Henderson, and D. Taylor, *J. Chem. Soc. (London), 1953*, 1281.
60. Castells, J., E. R. H. Jones, R. W. J. Williams, and G. D. Meakins, *Proc. Chem. Soc. (London), 1958*, 8.
60a. Cava, M. P., R. L. Litle, and D. R. Napier, *J. Am. Chem. Soc., 80*, 2257 (1958).
61. Chapman, O. L., and D. J. Pasto, *J. Am. Chem. Soc., 80*, 6685 (1958).
62. Chardonnens, L., and P. Heinrich, *Helv. Chim Acta, 32*, 656 (1949).
63. Ciamician, G., and P. Silber, *Ber., 33*, 2911 (1900).
64. Ciamician, G., and P. Silber, *Ber., 34*, 1530 (1901).
65. Ciamician, G., and P. Silber, *Ber., 34*, 2040 (1901).
66. Ciamician, G., and P. Silber, *Ber., 35*, 4128 (1902).
67. Ciamician, G., and P. Silber, *Ber., 36*, 4266 (1903).
68. Ciamician, G., and P. Silber, *Ber., 41*, 1071 (1908).
69. Ciamician, G., and P. Silber, *Ber., 41*, 1928 (1908).
70. Ciamician, G., and P. Silber, *Ber., 42*, 1510 (1909).
71. Ciamician, G., and P. Silber, *Ber., 43*, 945 (1910).
72. Ciamician, G., and P. Silber, *Ber., 43*, 1340 (1910).
73. Ciamician, G., and P. Silber, *Ber., 43*, 1536 (1910).
74. Ciamician, G., and P. Silber, *Ber., 44*, 1280 (1911).
75. Ciamician, G., *Science, 36*, 385 (1912).
76. Ciamician, G., and P. Silber, *Ber., 46*, 3077 (1913).
77. Ciusa, R., *Atti reale accad. nazl. Lincei*, (v), *15*, *ii* 721 (1906) [through *J. Chem. Soc., 92*, 137 (1907)].
78. Clar, E., and W. Müller, *Ber., 63*, 869 (1930).
79. Clar, E., *Ber., 82*, 495 (1949).
80. Cocker, W., K. Crowley, J. T. Edward, T. B. McMurry, and E. R. Stuart, *J. Chem. Soc. (London), 1957*, 3416.
81. Cohen, W. D., *Rec. trav. chim., 39*, 243 (1920).
82. Cookson, R. C., E. Crundwell, and J. Hudec, *Chem. and Ind. (London), 1958*, 1003.
83. Cookson, R. C., and E. Crundwell, *Chem. and Ind. (London), 1958*, 1004.
84. Cookson, R. C., and J. Hudec, *Proc. Chem. Soc. (London), 1959*, 11.
85. Corey, E. J., and W. R. Hertler, *J. Am. Chem. Soc., 80*, 2903 (1958).
86. Corey, E. J., and R. W. White, *J. Am. Chem. Soc., 80*, 6686 (1958).
87. Cristol, S. J., and R. L. Snell, *J. Am. Chem. Soc., 76*, 5000 (1954); *80*, 1950 (1958).

88. Cumming, W. M., and G. S. Ferrier, *J. Chem. Soc.* (*London*), *127*, 2374 (1925).
89. Dale, J., and L. Zechmeister, *J. Am. Chem. Soc.*, *75*, 2379 (1953).
90. Dauben, W. G., and G. J. Fonken, *J. Am. Chem. Soc.*, *79*, 2971 (1957).
91. Dauben, W. G., I. Bell, T. W. Hutton, G. F. Laws, A. Rheiner, and H. Urscheler, *J. Am. Chem. Soc.*, *80*, 4116 (1958).
92. Davis, W., and W. A. Noyes, *J. Am. Chem. Soc.*, *69*, 2153 (1947).
93. Davis, W., *Chem. Revs.*, *40*, 201 (1947).
94. Dev, S., *J. Indian Chem. Soc.*, *30*, 729 (1953).
95. Dilthey, W., and F. Quint, *Ber.*, *69*, 1575 (1936).
96. Dimroth, K., M. Bohlmann, and F. Bohlmann, *Angew. Chem.*, *59*, 176 (1947).
97. Doering, W. von E., and L. H. Knox, *J. Am. Chem. Soc.*, *72*, 2305 (1950); *75*, 297 (1953).
98. Doering, W. von E., J. R. Mayer, and C. H. de Puy, *J. Am. Chem. Soc.*, *75*, 2386 (1953).
99. Dost, N., and K. Van Nes, *Rec. trav. chim.*, *70*, 403 (1951).
100. Dutler, H., H. Bosshard, and O. Jeger, *Helv. Chim. Acta*, *40*, 494 (1957).
101. Eckert, A., *Ber.*, *58*, 322 (1925).
102. Emmons, W. E., *J. Am. Chem. Soc.*, *79*, 5739 (1957).
103. Esterle, J. G., P. M. Girling, P. de Mayo, and R. H. Wiley, unpublished observations.
104. Etienne, A., *Traité de Chimie Organique*, Vol. XVII, Masson, Paris, 1944, p. 1299.
105. Etienne, A., and A. Staehelm, *Bull. soc. chim. France*, *1959*, 748, and other papers in this series.
106. Fieser, L., and M. Fieser, *Steroids*, Reinhold, New York, 1959, p. 124.
107. Fischer, E., and Y. Frei, *J. Chem. Phys.*, *27*, 808 (1957).
108. Forbes, E. J., *J. Chem. Soc.* (*London*), *1955*, 3864.
109. Frankel, M., R. Wolovsky, and E. Fischer, *J. Chem. Soc.* (*London*), *1955*, 3441.
110. Fuller, G., and F. F. Rust, *J. Am. Chem. Soc.*, *80*, 6149 (1958).
111. Fulton, J. D., *Brit. J. Pharmacol.*, *3*, 75 (1948).
112. Gardner, P. D., R. L. Brandon, and G. R. Haynes, *J. Am. Chem. Soc.*, *79*, 6334 (1957).
113. Glasstone, S., K. J. Laidler, and H. Eyring, *The Theory of Rate Processes*, McGraw-Hill, New York, 1941, pp. 323 *ff.*
114. Greene, F. D., S. L. Misrock, and J. R. Wolfe, *J. Am. Chem. Soc.*, *77*, 3852 (1955).
115. Greuter, F., J. Kalvoda, and O. Jeger, *Proc. Chem. Soc.* (*London*), *1958*, 349.
116. Grignard, V., and Tchéoufaki, *Rec. trav. chim.*, *48*, 899 (1929); cf. Strauss, F., *Ann.*, *342*, 190 (1905).
117. Grummitt, O., and F. J. Christoph, *J. Am. Chem. Soc.*, *71*, 4157 (1949).
118. Guia, M., and M. Civera, *Gazz. chim. ital.*, *81*, 875 (1951).
119. Gutsche, C. D., and H. E. Johnson, *J. Am. Chem. Soc.*, *77*, 5933 (1955).
120. Hartley, G. S., *J. Chem. Soc.* (*London*), *1938*, 633.
121. Havinga, E., A. Verloop, and A. L. Koevoet, *Rec. trav. chim.*, *75*, 371 (1956).

122. Helferich, B., and E. von Gross, *Chem. Ber.*, *85*, 531 (1952); Helferich, B., E. N. Mucahy, and H. Ziegler, *Chem. Ber.*, *87*, 233 (1954); Helferich, B., and M. Gindy, *Chem. Ber.*, *87*, 1488 (1954).
123. Horner, L., and H. Merz, *Ann.*, *570*, 89 (1950).
124. Horner, L., E. Spietschka, and A. Gros, *Ann.*, *573*, 17 (1951).
125. Horner, L., and E. Spietschka, *Chem. Ber.*, *85*, 255 (1952).
126. Horner, L., and H. Stöhr, *Chem. Ber.*, *85*, 993 (1952).
127. Horner, L., E. Spietschka, and E. Becker, *Chem. Ber.*, *88*, 934 (1955).
128. Horner, L., and E. Jürgens, *Chem. Ber.*, *90*, 2184 (1957).
129. Huisgen, R., *Ann*, *564*, 16 (1949).
130. Inhoffen, H. H., F. Bohlmann, and G. Rummert, *Ann.*, *571*, 75 (1951).
131. Inhoffen, H. H., and H. Siemer, *Fortschritte der Chemie organischer Naturstoffe*, Vol. IX, Springer-Verlag, Vienna, 1952, p. 1.
132. Inhoffen, H. H., K. Bruckner, K. Irmscher, and G. Quinkert, *Chem. Ber.*, *88*, 1424 (1955).
133. Inhoffen, H. H., G. Quinkert, H-J. Hess, and H-M. Erdmann, *Chem. Ber.*, *89*, 2273 (1956).
134. Isidate, M., and M. Yoshida, *Pharm. Bull.* (*Tokyo*), *4*, 43 (1956).
135. Jeger, O., J. Redel, and R. Nowak, *Helv. Chim. Acta*, *29*, 1241 (1946).
136. Jong, A. W. K. de, *Rec. trav. chim.*, *43*, 316 (1924).
137. Jonge, J. de, and R. Dijkstra, *Rec. trav. chim.*, *67*, 328 (1948).
138. Jonge, J. de, and R. Dijkstra, *Rec. trav. chim.*, *68*, 426 (1949); Jonge, J. de, R. Dijkstra, and G. L. Wiggenink, *Rec. trav. chim.*, *71*, 846 (1952); and other papers.
139. Jonge, J. de, and R. Dijkstra, *Rec. trav. chim.*, *75*, 290 (1956).
140. Kamlet, M., and L. Kaplan, *J. Org. Chem.*, *22*, 576 (1957).
141. Kenyon, J., A. Rassoul, and G. Soliman, *J. Chem. Soc.* (*London*), *1956*, 1774.
142. Kharasch, M. S., and H. N. Friedlander, *J. Org. Chem.*, *14*, 245 (1949).
143. Kharasch, M. S., W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, *14*, 248 (1949).
144. Kharasch, M. S., and R. H. Snyder, *J. Org. Chem.*, *14*, 819 (1949).
145. Kharasch, M. S., G. Stampa, and W. Nudenberg, *Science*, *116*, 309 (1952).
146. Kharasch, M. S., J. Kuderna, and W. Nudenberg, *J. Org. Chem.*, *18*, 1225 (1953).
147. Kirmse, W., and L. Horner, *Chem. Ber.*, *89*, 2759 (1956).
148. Kistiakowsky, G. B., and S. W. Benson, U. S. Pat. 2,414,880 [through *Chem. Abstr.*, *41*, 3483 (1947)].
149. Klinger, H., *Ann.*, *249*, 137 (1888); Klinger, H., and W. Standke, *Ber.*, *24*, 1340 (1891); Klinger, H., and W. Kolvenbach, *Ber.*, *31*, 1214 (1898).
150. Koizumi, M., Z. Watanabe, and A. Kuroda, *Nature*, *175*, 770 (1955).
151. Kröhnke, F., G. Kröhnke, and I. Vogt, *Chem. Ber.*, *86*, 1500 (1953).
152. Kröhnke, F., *Ann.*, *604*, 203 (1957).
153. Kuchler, L., and F. Patat, *Z. Electrochem.*, *42*, 529 (1936).
154. Landquist, J. K., *J. Chem. Soc.* (*London*), *1953*, 2830.
155. Leighton, P. A., and F. A. Lucy, *J. Chem. Phys.*, *2*, 756, 760 (1934).
156. Lettré, H. H., in *Sterine, Gallensäuren und verwandte Naturstoffe*, Vol. I, F. Enke Verlag, Stuttgart, 1954.

157. Lewis, G. N., T. T. Magel, and D. Lipkin, *J. Am. Chem. Soc., 62,* 2973 (1940).
158. Limaye, D. B., *J. Univ. Bombay,* I, Pt. 2, 52 (1932) [through *Chem. Abstr., 27,* 2097 (1933)].
159. Lund, K., and L. Zechmeister, *J. Am. Chem. Soc., 76,* 2308 (1954).
160. Lutz, R. E., P. S. Bailey, Chi-Kang Dien, and J. Riniker, *J. Am. Chem. Soc., 75,* 5039 (1953).
161. Mahncke, H. E., and W. A. Noyes, *J. Am. Chem. Soc., 58,* 932 (1936).
162. Makhailov, B. M., and G. S. Tersarkisyan, *Bull. Acad. Sci. U.S.S.R.,* 656 (1954) [through *Chem. Abstr., 49,* 10953 (1955)].
163. Manning, P. P., *J. Am. Chem. Soc., 79,* 5151 (1957).
164. Masson, C. R., *J. Am. Chem. Soc., 74,* 4731 (1952).
165. Masson, C. R., V. Boekelheide, and W. A. Noyes in *Catalytic, Photochemical, and Electrolytic Reactions* (Vol. II of A. Weissberger, ed., *Technique of Organic Chemistry*), 2nd ed., Interscience, New York–London, 1956, pp. 257–384.
166. Mayo, P. de, and W. Templeton, unpublished observations.
167. McNesby, J. R., and A. S. Gordon, *J. Am. Chem. Soc., 80,* 261 (1958).
168. Meerwein, H., H. Disselnkötter, F. Rappen, H. v. Rintelen, and H. Van de Vloed, *Ann., 604,* 151 (1957).
169. Meyer, H., and A. Eckert, *Monatsh., 39,* 243 (1918).
170. Mochel, W. E., J. L. Crandall, and J. H. Peterson, *J. Am. Chem. Soc., 77,* 494 (1955).
171. Moore, A. M. and C. H. Thomson, *Can. J. Chem., 35,* 163 (1957).
172. Moore, R. F., and W. A. Waters, *J. Chem. Soc. (London), 1953,* 238.
173. Mustafa, A., and A. M. Islam, *J. Chem. Soc. (London), 1949,* S81.
174. Mustafa, A., *J. Chem. Soc. (London), 1949,* S. 83.
175. Mustafa, A., *J. Chem. Soc. (London), 1951,* 1034.
176. Mustafa, A., *Chem. Revs., 51,* 1 (1952).
177. Mustafa, A., and M. Kamel, *J. Am. Chem. Soc., 77,* 5630 (1955).
178. Mustafa, A., A. H. E. Harhash, A. K. E. Mansour, and S. M. A. E. Omran, *J. Am. Chem. Soc., 78,* 4306 (1956).
179. Nicholson, A. J. C., *Revs. Pure and Appl. Chem. (Australia), 2,* 174 (1952).
180. Nicholson, A. J. C., *Trans. Faraday Soc., 50,* 1067 (1954).
181. Norrish, R. G. W., and M. E. S. Appleyard, *J. Chem. Soc. (London), 1934,* 874; and later papers.
182. Noyes, W. A., and L. M. Dorfmann, *J. Chem. Phys., 16,* 788 (1948).
183. Noyes, W. A., G. B. Porter, and J. E. Jolley, *Chem. Revs., 56,* 49 (1956).
184. Oliveri-Mandala, E., G. Caronna, and E. Deleo, *Gazz. chim. ital., 68,* 324 (1938).
185. Olson, A. R., and F. L. Hudson, *J. Am. Chem. Soc., 55,* 1410 (1933).
186. Olson, A. R., *J. Chem. Phys., 1,* 418 (1933).
187. Olson, A. R., and W. Maroney, *J. Am. Chem. Soc. 56,* 1320 (1934).
188. Owades, J. L., *Experientia, 6,* 258 (1950).
189. Pailer, M., and U. Miller, *Monatsh., 79,* 615 (1948).
190. Parker, C. O., and P. E. Spoerri, *Nature, 166,* 603 (1950).
191. Paterno, E., *Gazz. chim. ital., 39b,* 237 (1906).

192. Paterno, E., and G. Chieffi, *Gazz. chim. ital., 39b*, 341 (1909).
193. Paterno, E., and G. Chieffi, *Gazz. chim. ital., 39b*, 415 (1909).
194. Paterno, E., *Gazz. chim. ital., 44*, 151 (1914).
195. Pelletier, S. W., and E. L. McLeish, *J. Am. Chem. Soc., 74*, 6292 (1952).
196. Pfeiffer, P., *Ber., 45*, 1819 (1912).
197. Pfeiffer, P., *Ann., 411*, 72 (1916).
198. Pieck, R., and E. W. R. Steacie, *Can. J. Chem., 33*, 1304 (1955).
199. Pitts, J. N., R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald, and R. B. Martin, *J. Am. Chem. Soc., 81*, 1068 (1958).
200. Rappoldt, M. P., P. Westerhof, K. H. Hanewald, and J. A. K. Buisman, *Rec. trav. chim., 77*, 241 (1958).
201. Rappoldt, M. P., J. A. K. Buisman, and E. Havinga, *Rec. trav. chim., 77*, 327 (1958).
202. Reid, C., *Excited States in Chemistry and Biology*, Butterworths Scientific Pub., London, 1957.
203. Reid, C., Ref. 202, p. 78.
204. Reid, W., and M. Wilk, *Ann., 590*, 91, 111 (1954).
205. Reimer, M., *J. Am. Chem. Soc., 46*, 783 (1924).
206. Roebber, J. L., G. K. Rollefson, and G. C. Pimentel, *J. Am. Chem. Soc., 80* 225 (1958).
207. Rollefson, G. K., and M. Burton, *Photochemistry and the Mechanism of Chemical Reactions*, Prentice-Hall, New York, 1939.
208. Rollefson, G. K., and M. Burton, Ref. 208, p. 248.
209. Sachs, F., and R. Kempf, *Ber., 35*, 2704 (1902).
210. Saltmarsh, O. D., and R. G. W. Norrish, *J. Chem. Soc. (London), 1935*, 455.
211. Šantavý, F., *Collection Czechoslov. Chem. Communs., 16*, 665 (1951).
212. Schenk, G. O., *Naturwissenschaften, 40*, 229 (1953); *Angew. Chem., 64*, 12 (1952); and many other papers in this series.
213. Schenk, G. O., and G. A. Schmidt-Thomé, *Ann., 584*, 199 (1953).
214. Schenk, G. O., and H. Ziegler, *Ann., 584*, 221 (1953).
215. Schenk, G. O., *Dechema Monograph., 24*, 105 (1955).
216. Schenk, G. O., G. Koltzenburg, and H. Grossman, *Angew. Chem., 69*, 588 (1957).
217. Schlubach, H. H., V. Franzen, and E. Dahl, *Ann., 587*, 124 (1954).
218. Scholl, R., *Monatsh., 34*, 1011 (1913); Preuss, L., and A. Binz, *Z. Angew. Chem., 13*, 385 (1900).
219. Schönberg, A., and R. Moubasher, *J. Chem. Soc. (London), 1939*, 1430.
220. Schönberg, A., and A. Mustafa, *J. Chem. Soc. (London), 1943*, 276.
221. Schönberg, A., and A. Mustafa, *J. Chem. Soc., (London), 1944*, 67.
222. Schönberg, A., and R. Moubasher, *J. Chem. Soc. (London) 1944*, 366.
223. Schönberg, A., and A. Mustafa, *J. Chem. Soc. (London), 1944*, 387.
224. Schönberg, A., and W. I. Awad, *J. Chem. Soc. (London), 1945*, 197; *1947*, 651.
225. Schönberg, A., and A. Mustafa, *J. Chem. Soc. (London), 1945*, 551.
226. Schönberg, A., A. F. Ismail, and W. Asker, *J. Chem. Soc. (London), 1946*, 442.

227. Schönberg, A., and A. Mustafa, *Chem. Revs.*, *40*, 181 (1947).
228. Schönberg, A., and A. Mustafa, *J. Chem. Soc.* (*London*), *1947*, 997.
229. Schönberg, A., A. Mustafa, M. Z. Barakan, N. Latif, and R. Moubasher, *J. Chem. Soc.* (*London*), *1948*, 2126.
230. Schönberg, A., N. Latif, R. Moubasher, and W. I. Awad, *J. Chem. Soc.* (*London*), *1950*, 374.
231. Schönberg, A., and N. Latif, *J. Am. Chem. Soc.*, *72*, 4828 (1950).
232. Schönberg, A., N. Latif, R. Moubasher, and A. Sina, *J. Chem. Soc.* (*London*), *1951*, 1364.
233. Schönberg, A., and N. Latif, *J. Chem. Soc.* (*London*), *1952*, 446.
234. Schönberg, A., W. I. Awad, and G. A. Mousa, *J. Am. Chem. Soc.*, *77*, 3850 (1955).
235. Schönberg, A., A. K. Fateen, and S. M. A. E. Omran, *J. Am. Chem. Soc.*, *78*, 1224 (1956).
236. Schönberg, A., and M. M. Sidky, *J. Org. Chem.*, *22*, 1698 (1957).
237. Schönberg, A., *Präparative Organische Photochemie*, Springer-Verlag, Berlin, 1958.
238. Secareanu, S., and I. Lupas, *Bull. soc. chim. France*, *1936*, 1161.
239. Simons, J. P., *Quart. Revs.* (*London*), *13*, 3 (1959).
240. Simonsen, J. L., and D. H. R. Barton, *The Terpenes*, Vol. III, Cambridge Univ. Press, Cambridge, 1952, p. 292.
241. Sircar, A. C., and S. C. Sen, *J. Indian Chem. Soc.*, *8*, 605 (1931).
242. Smith, P., and B. B. Brown, *J. Am. Chem. Soc.*, *73*, 2435 (1951).
243. Splitter, J. S., and M. Calvin, *J. Org. Chem.*, *20*, 1086 (1955).
244. Splitter, J. S., and M. Calvin, *J. Org. Chem.*, *23*, 651 (1958).
245. Staudinger, H., and St. Bereza, *Ann.*, *380*, 243 (1911).
246. Stobbe, H., *Ber.*, *40*, 3372 (1907).
247. Stobbe, H., and A. Lehfeldt, *Ber.*, *58*, 2415 (1925).
248. Stobbe, H., and K. Bremer, *J. prakt. Chem.*, *123*, 1 (1929).
249. Stoermer, R., *Ber.*, *42*, 4865 (1909).
250. Stoermer, R., *Ber.*, *44*, 637 (1911).
251. Stoermer, R., *Ber.*, *44*, 667 (1911).
252. Stoermer, R., and H. Stockmann, *Ber.*, *47*, 1786 (1914).
252a. Stoermer, R., and H. Stockmann, *Ber.*, *47* 1793 (1914).
253. Stoermer, R., and H. Ladewig, *Ber.*, *47*, 1795 (1914).
254. Stoermer, R., and H. Oehlert, *Ber.*, *55*, 1232 (1922).
255. Stoll, A., and W. Schlientz, *Helv. Chim. Acta*, *38*, 585 (1955).
256. Suida, H., *J. prakt. Chem.*, *84*, 829 (1911).
257. Süs, O., *Ann.*, *556*, 65 (1944).
258. Süs, O., *Ann.*, *557*, 237 (1947).
259. Süs, O., *Ann.*, *579*, 133 (1953).
260. Süs, O., M. Glos, K. Möller, and H-D. Eberhardt, *Ann.*, *583*, 150 (1953).
261. Süs, O., K. Möller, and H. Heiss, *Ann.*, *598*, 123 (1956).
262. Süs, O., and K. Möller, *Ann.*, *599*, 233 (1956); *593*, 91 (1955).
263. Tanasescu, I., *Bull. soc. chim. France*, *1926*, 1443.
264. Tanasescu, I., *Bull. soc. chim. France*, *1927*, 1074.
265. Tanasescu, I., and M. Ionescu, *Bull. soc. chim. France*, *1940*, 84.

266. Tanasescu, I., and F. Hodosan, *Acad. rep. populare Romîne, Bul. stiint., Sect. Stiinte technice şi chim., 5*, 37 (1953); through *Chem. Abstr., 50*, 14628 (1956).
267. Treibs, W., *J. prakt. Chem., 138*, 299 (1930).
268. Uri, N., *J. Am. Chem. Soc., 74*, 5808 (1952).
269. Urry, W. H., and J. R. Eiszner, *J. Am. Chem. Soc., 74*, 5882 (1952).
270. Urry, W. H., F. W. Stacey, O. O. Juveland, and C. H. McDonnell, *J. Am. Chem. Soc., 75*, 250 (1953).
271. Urry, W. H., F. W. Stacey, E. S. Huyser, and O. O. Juveland, *J. Am. Chem. Soc., 76*, 450 (1954).
272. Utzinger, E., H. Dutler, K. Weinberg, D. Arigoni, and O. Jeger, *Angew. Chem., 71*, 80 (1959).
273. Van Tamelen, E. E., S. H. Levin, G. Brenner, J. Wolinsky, and P. Aldrich, *J. Am. Chem. Soc., 80*, 501 (1958).
274. Velluz, L., and G. Amiard, *Compt. rend., 692*, 853 (1949); and other papers in this series.
275. Velluz, L., G. Amiard, and A. Petit, *Bull. soc. chim., France, 1949*, 501.
276. Velluz, L., G. Amiard, and B. Goffinet, *Bull. soc. chim. France, 1955*, 1341.
277. Velluz, L., B. Goffinet, and G. Amiard, *Tetrahedron, 4*, 241 (1958).
278. Venkataraman, K., *The Chemistry of Synthetic Dyes*, Academic Press, New York, 1952, p. 1217.
279. Verloop, A., A. L. Koevoet, and E. Havinga, *Rec. trav. chim., 76*, 689 (1957).
280. Vliervoet, J. L. J. van de, P. Westerhof, J. A. K. Buisman, and E. Havinga, *Rec. trav. chim., 75*, 1179 (1956).
281. Wang, S. Y., M. Apicella, and B. R. Stone, *J. Am. Chem. Soc., 78*, 4180 (1956).
282. Weizmann, C., E. Bergmann, and Y. Hirshberg, *J. Am. Chem. Soc., 60*, 1530 (1938).
283. Wells, C. F., *Nature, 177*, 483 (1956).
284. Westerhof, P., and J. A. K. Buisman, *Rec. trav. chim., 75*, 1243 (1956).
285. Wheeler, J. W., and R. H. Eastman, *J. Am. Chem. Soc., 81*, 236 (1959).
286. Wiberg, K. B., and T. W. Hutton, *J. Am. Chem. Soc., 76*, 5367 (1954).
287. Wiegand, C., and F. Merkel, *Ann., 550*, 175 (1942).
288. Windaus, A., and P. Borgeaud, *Ann., 460*, 235 (1928).
289. Windaus, A., J. Gaede, J. Köser, and G. Stein, *Ann., 483*, 17 (1930).
290. Woodward, R. B., N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc., 67*, 1425 (1945).
291. Woodward, R. B., and T. Singh, *J. Am. Chem. Soc., 72*, 494 (1950).
292. Wyman, G. M., *Chem. Revs., 55*, 625 (1955).
293. Yang, N. C., and D-D. H. Yang, *J. Am. Chem. Soc., 80*, 2913 (1958).
294. Yates, P., and M. J. Jorgensen, *J. Am. Chem. Soc., 80*, 6150 (1958).
295. Zavarin, E., *J. Org. Chem., 23*, 47 (1958).
296. Zechmeister, L., O. Frehden, and P. F. Jorgensen, *Naturwissenschaften, 26*, 495 (1938).
297. Zechmeister, L., and A. L. Rosen, *J. Am. Chem. Soc., 64*, 2755 (1942).
298. Zechmeister, L., and H. J. Pinkard, *J. Am. Chem. Soc., 76*, 4144 (1954); see also Zechmeister, L., *Experientia, 10*, 1 (1954).

299. The author is indebted to Professor R. B. Woodward (Harvard) and to Professor D. H. R. Barton (Imperial College) for valuable discussions of this point.
300. Mayo, P. de, and J. B. Stothers, unpublished observations.
301. Mayo, P. de, J. B. Stothers, and W. Templeton, *Proc. Chem. Soc.* (*London*), *1960*, 72.
302. Blair, J. M., D. Bryce-Smith, and B. W. Pengilly, *J. Chem. Soc.* (*London*), *1959*, 3174.
303. Arigoni, D., D. H. R. Barton, R. Bernasconi, C. Djerassi, J. S. Mills, and R. Wolf, *Proc. Chem. Soc.* (*London*), *1959*, 306.
304. Angus, H. F. J., and D. Bryce-Smith, *Proc., Chem. Soc.* (*London*), *1959*, 326.
305. Blair, J. M., and D. Bryce-Smith, *Proc. Chem. Soc.* (*London*), *1959*, 287.
306. Forbes, E. J., and R. A. Ripley, *J. Chem. Soc.* (*London*), *1959*, 2770.
307. Dauben, W. G., K. Koch, and W. E. Thiessen, *J. Am. Chem. Soc.*, *81*, 6088 (1959).
308. Hurst, J. J., and G. H. Whitham, *Proc. Chem. Soc.* (*London*), *1959*, 160.
309. Kläning, U. K., and M. C. R. Symons, *Proc. Chem. Soc.* (*London*), *1959*, 95.
310. Dauben, W. G., and J. A. Ross, *J. Am. Chem. Soc.*, *81*, 6522 (1959).
311. Hammond, G. S., and W. M. Moore, *J. Am. Chem. Soc.*, *81*, 6334 (1959).
312. Srinivasan, R., *J. Am. Chem. Soc.*, *81*, 5541 (1959), and other earlier papers in this series.
313. Ausloos, P., and E. Murad, *J. Am. Chem. Soc.*, *80*, 5929 (1958).
314. Inscoe, M. N., J. H. Gould, and W. R. Brode, *J. Am. Chem. Soc.*, *81*, 5634 (1959).
315. Margerum, J. D., J. N. Pitts, J. G. Rutgers, and S. Searles, *J. Am. Chem. Soc.*, *81*, 1549 (1959).
316. House, H. O., *J. Org. Chem.*, *24*, 1374 (1959).
317. Bird, C. W., and R. C. Cookson, *J. Org. Chem.*, *24*, 441 (1959).
318. Parham, W. E., P. L. Stright, and W. R. Hasek, *J. Org. Chem.*, *24*, 262 (1959).
319. Lindenfors, S., *Arkiv Kemi*, *14*, 227 (1959).
320. Calas, R., and R. Lalande, *Bull. soc. chim. France*, *1959*, 1770, and other papers in this series.
321. Horner, L., K. Muth, and H.-G. Schmelzer, *Chem. Ber.*, *92*, 2953 (1959).
322. Kirmse, W., *Angew Chem.*, *71*, 537 (1959).
323. Müller, E., H. Metzger, D. Fries, U. Heuschkel, K. Witte, E. Waidelich, and G. Schmid, *Angew. Chem.*, *71*, 229 (1959).
324. Yang, N. C., private communication, 1960.
325. Buchschacher, P., M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, *42*, 2122 (1959).
326. Schenk, G. O., and H. Ziegler, *Naturwissenschaften*, *32*, 157 (1944); Schenk, G. O., K. G. Kinkel, and H.-J. Mertens, *Ann.*, *584*, 125 (1953).
327. Nickon, A., and J. F. Bagli, *J. Am. Chem. Soc.*, *81*, 6330 (1959).
328. Alder, K., R. Muders, W. Krane, and P. Wirtz, *Ann.*, *627*, 59 (1959).
329. de Kock, R. J., Dissertation, Leiden, April 22, 1959.
330. de Kock, R. J., N. G. Minnaard, and E. Havinga, *Rec. trav. chim.*, *79* (in press, 1960).
331. Inhoffen, H. H., and K. Irmscher, *Fortschritte der Chemie organische Naturstoffe*, Vol. XVII, Springer-Verlag, Vienna, 1959, p. 70.

THE CHEMISTRY OF MUSCARINE

BY C. H. EUGSTER,* *Chemical Institute, University of Zürich*

CONTENTS

I. Introduction 427
II. Isolation of Muscarine from *Amanita muscaria* and *Inocybe patouillardi* 428
III. Structural Investigations of Muscarine 435
A. The Nitrogen Function 435
B. The Oxygen Functions 436
C. The Carbon Skeleton 437
IV. Syntheses of Muscarine and Its Stereoisomers 440
A. Synthesis of D- and L-Muscarine from Chitaric Acid 441
B. Syntheses via Tetrahydrofuranones 442
C. Ring Closure of 1,4-Diols to Substituted Tetrahydrofurans 444
D. Synthesis of All Muscarine Isomers from Furan Derivatives 446
E. Resolution of Racemic Muscarine Chloride into Its Antipodes 453
References 453

I. Introduction

Muscarine is an alkaloid which was originally isolated from fly agaric [(*Amanita muscaria* (L. ex Fr.) Quél.)]. It has for a long time attracted the attention of pharmacologists and chemists because of its marked and peculiar action on the autonomic nervous system. It must, however, be said in retrospect that investigations in the muscarine field over the past 150 years have until very recently formed a sequence of errors and disappointments, with only infrequent intervention of meaningful experiment and observation. One might say that almost every chemist who has ever approached the muscarine problem has "burnt his fingers" on it. The small size and relatively simple structure of the molecule stand in marked contrast to the great exertions that have attended its investigation. The main reason in most cases has been the fact that muscarine was, until recently, one of the most difficultly accessible substances among natural products from plants; only the advent of modern methods of separation has made it possible to prepare pure muscarine salts.

* Translated by Dr. K. H. Overton, The University, Glasgow, Scotland.

It is, however, not the author's intention to write a chronicle of muscarine research nor even to touch on its physiological and pharmacological aspects. It is intended merely to present a survey of the interesting chemistry of muscarine, such as has become possible as a result of the combined endeavors of a number of schools.

II. Isolation of Muscarine from *Amanita muscaria* and *Inocybe patouillardi*

It is difficult today to assess the purity of the muscarine concentrates prepared by early workers, since in most cases neither analyses nor melting points are quoted for the salts that were isolated. Nor is it possible to infer the muscarine content of these preparations with any certainty from the biological data because of the diversity of methods used and their large margins of error. Moreover, it is now known that the highly active acetylcholine invariably accompanies muscarine in extracts of *Amanita muscaria* (30). It seems probable that the preparations of Schmiedeberg and Koppe (38), Harnack (24), and Nothnagel (36) contained at best 20% of muscarine. The main contaminant was undoubtedly choline. The muscarine tetrachloroaurates of Honda (25) and H. King (27) appear to have been considerably purer, as can be judged from a gold determination of King. His yield of muscarine was, however, surprisingly high. The preparations of Kögl and his associates, described in 1931 (28), are now known to have been in part seriously contaminated with acetylcholine (30). The recorded rotation of the (oily) chloride amounted to only about 25% in terms of the pure salt; accordingly, the analyses led to the wrong empirical formula. A later preparation isolated by the same author (1942) (29) appears to have been considerably purer in spite of its low physiological activity, as can be judged from the melting point of the tetrachloroaurate, here recorded for the first time.

However, it can be seen in the light of present knowledge that none of the earlier workers could have obtained really pure muscarine with the methods available to them. The isolation of crystalline muscarine chloride, which appears to afford a good and reliable criterion of purity, was first accomplished in 1954 (8). To be sure, preparation of the chloride was considerably facilitated by the experiences of earlier authors, particularly their mention of the easy solubility of muscarine in alcohol, its insolubility in ether (38), its precipitation with $KBiI_4$

and $KHgI_4$ (38), as well as with phosphotungstic acid (27,38), Reinecke's acid (28), etc. The observation that muscarine is adsorbed on charcoal from aqueous solution only very slightly or not at all and that it is stable to dilute alkali (27) was also valuable. Muscarine was further assumed to be very readily oxidized, particularly in acid solution (28), a fact to be taken into account for any new isolation.

The procedure adopted by us for isolation of muscarine from fly agarics was to crush the fresh fungus finely under alcohol in a high-powered mincing machine immediately on delivery in order to preclude fermentative changes (8,9). After filtration the aqueous alcoholic extracts were carefully concentrated and the sirup separated into fractions, one easily and the other sparingly soluble in absolute alcohol. After concentration of the easily soluble fraction, the residue was dissolved in water and defatted with ether. At this point muscarine could be isolated, along with a mixture of other bases, as the Reineckate. After the usual decomposition of the Reineckates, the crude chlorides were chromatographed over large cellulose columns using a number of solvent systems. The enrichment at all stages was followed by means of tests on the isolated frog heart (8,9,39).

Some remarks are indicated regarding the decomposition of the chloroaurates. When these salts are decomposed according to the usual procedure of Dudley (7) with silver powder, muscarine undergoes a partial transformation, whose chemical nature has not been investigated further but which results in serious loss of activity. A large number of experiments with anion exchangers of widely differing type also led to considerable loss of biological activity. The hydrogen sulfide method, on the other hand, leads to negligible losses, as could be demonstrated in separate experiments.

The various stages in the work-up procedure and the enrichments achieved are shown on page 430.

After a repetition of column chromatography, the muscarine was sufficiently pure (particularly, free of choline) to be readily crystallizable as the tetrachloroaurate. Decomposition of the aurate with hydrogen sulfide afforded the chloride which, after the appropriate drying in high vacuum, was obtained crystalline for the first time.

The final yields of crystalline muscarine chloride were at least of the order of 70%, based on the biologically estimated muscarine content of the fresh fungus. The actual yield is probably even higher, since the presence of acetylcholine in the fungus indicates a higher

Working-up Procedure

Fungus material
(124 kg., fresh)

↓ Crushed in a Turmix disintegrator under ethanol, filtered; extraction with alcoho repeated.

Ethanol extracts

↓ Concentrated to syrup in partial vacuum; three precipitations with absolute alcohol.

Fraction easily soluble in ethanol + fraction sparingly soluble in ethanol (discarded)

↓ Residue dissolved in water; concentration in partial vacuum; defatting with ether.

Aqueous concentrates

↓ Precipitation from solution in dilute acetic acid with aqueous ammonium Reineckate.

Reineckate precipitate + mother liquors (discarded)
(105.4 g. Reineckates)

↓ Separation into acetone-soluble and acetone-insoluble fractions; decomposition of the acetone-soluble after Kapfhammer (acetone-insoluble material discarded).

Crude chlorides
(28.9 g.; enrichment 1:4300)

↓ First partition chromatogram with *n*-butanol–pyridine–water (80:16:25).

Muscarine concentrate
(6.4 g.; enrichment 1:19,400)

↓ Second partition chromatogram with *n*-butanol equilibrated with aqueous ammonia.

Muscarine concentrate
(1.380 g.; enrichment 1:90,000)

↓ Precipitation with chloroauric acid.

Crystalline tetrachloroaurate
(crude 913 mg. = 370 mg. muscarine chloride; enrichment 1:335,000)

↓ Decomposition with hydrogen sulfide, gold sulfide filtered off, chloride solution treated with animal charcoal, shaken with silver chloride suspension, filtration, concentration *in vacuo*, recrystallization of residue from isopropanol–acetone.

Muscarine chloride
(total yield 260 mg.; enrichment 1:480,000)

muscarine content than is the case. The enrichment achieved in the example cited was thus of the order 1:500,000, and with subsequent harvests of fungus it was actually substantially higher.

Fortunately, the authors (8,9) were soon able to correlate biological activity with a paper chromatographic procedure, which enabled them to dispense with time-consuming biological tests, resulting in the "incomparable facilitation" of subsequent work (31) (see Fig. 1 and Table I).

The recognition that pure muscarine is relatively stable made it possible to simplify the procedure just described. Thus it now seems

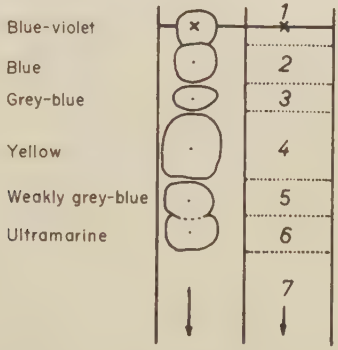


Fig. 1. Paper chromatogram of 25 crude chlorides. Solvent system, 7 (Table II); paper, Whatman No. 1; spraying reagent, bromocresol green. Also estimation of the separate zones on the frog heart. Activities are given in Table I.

TABLE I
Biological Activities Correlated with Chromatographic Zones of Figure 1

Zone no.	R_f	Activity, muscarine units
1	0	40
2	0.06	40
3	0.11	40
4	0.19	40
5	0.26	1000
6	0.31	5200
7	—	250

desirable to percolate the crude chlorides obtained from decomposition of the Reineckates through a strongly basic ion exchanger (e.g., Amberlite IRA-400, OH^-) prior to column chromatography (11). Muscarine travels very quickly through the column, while a considerable number of contaminants is retained. In addition, this procedure hydrolyzes the interfering acetylcholine.

It also no longer appears necessary to start with the fresh fungus; comparable yields of muscarine could be isolated from appropriately dried material (12).

A somewhat different procedure has been described by Kuehl, Lebel, and Richter (34). These authors treated a purified muscarine concentrate, obtained from fly agaric without recourse to the Reineckates, with much charcoal and obtained a further enrichment of muscarine by chromatography over weakly acid Amberlite IRC-50 (H^+) columns with 0.1*N* acetic acid as eluant. After repetition of this procedure, the concentrate was again treated with much charcoal and subjected to partition chromatography over kieselguhr using an acetic acid–butanol-water mixture. Muscarine chloride was obtained crystalline from the most active fractions. Melting points and yields were, however, not quoted.

In 1957 Kögl and his collaborators also succeeded in isolating crystalline muscarine chloride (30). They also used cellulose and Amberlite IRC-50 (H^+) columns for the separation of the crude chloride mixture obtained from the Reineckate fraction. The authors claim to have obtained better results with large Norit columns; however, two chromatograms were then necessary for the complete removal of choline. (In later work with synthetic mixtures these authors seem to have abandoned the use of Norit in favor of cellulose.) Yields of crystalline muscarine chloride were not recorded.

The experiments of K. Balenović and his collaborators for the preparation of muscarine also deserve mention (1). Their apparent failure to obtain crystalline muscarine chloride can probably be attributed to the fact that they decomposed the substantially pure tetrachloroaurate according to the procedure of Dudley (7) and chromatographed the chloride on strongly acid columns of Dowex 50 (H^+) in 2.5–4*N* hydrochloric acid. It is to be expected that muscarine would be decomposed under these conditions.

Crystalline muscarine has also been isolated in the Wellcome Research Laboratories (37) from fly agaric. Experimental details have not yet been published.

It should be possible to base a particularly effective isolation procedure on a combination of all the published methods; this could, for instance, be useful in the detection of muscarine in further species of fungi or in toxicological work. Specific precipitating agents have so far received little attention.

TABLE II
Solvent Systems[a]

No.	Solvent system	R_f values	Ref.
1	*n*-Butanol–pyridine–water (80:16:25)	0.20–0.22	8,9
2	*n*-Butanol–pyridine–water (8:3:4)	0.26	8,9
3	*n*-Butanol–pyridine–water (6:2:3)	0.24–0.26	1
4	*sec*-Butanol–ethanol (abs.)–acetic acid–water (15:5:1:5)	0.37–0.40	9
5	*n*-Butanol satd. with 1.5*N* NH_3 (20:5)	0.13–0.14	9
6	*n*-Butanol satd. with 1.5*N* NH_3	0.26 (?)	1
7	*sec*-Butanol–ethanol (95%)–1.5*N* NH_3 (15:5:5)	0.26–0.29	9
8	*n*-Butanol–ethanol–water (5:5:2)[b]	0.50	30
9	*n*-Butanol–dioxane (4:1) satd. with water	0.35	34
10	*n*-Butanol–acetic acid–water (4:1:5) (upper phase)	0.49	34
11	Methyl ethyl ketone–ethyl cellosolve–water (300:15:706)	0.19	34
12	Ethanol (95%)–NH_3 (conc.) (19:1)	0.50	34

[a] Whatman No. 1 paper.
[b] Paper not specified.

TABLE III
Spraying Reagents

Reagent	Comment
Dragendorff's reagent	Modified after (2,40) In our experience the reagent of choice. Spots appear with characteristic delay, being of flesh-red to brick-red tint on a yellow background. They are stable for a considerable time. Readily detects 6 γ of muscarine chloride (9).
Bromocresol green	Somewhat less sensitive, but very clear ultramarine spots on a green background (9).
Other reagents	Iodine vapor (9), dipicrylamine (9), Levine-Chargaff reagent (1).

TABLE IV
The Most Important Salts of Natural Muscarine

Salt	Melting point, °C.	Comments
Muscarine chloride, $(C_9H_{20}NO_2)^+Cl^-$· $(0H_2O, {}^1/_2H_2O, 1H_2O)$	181–182 (8,9) 180–181 (30)	Colorless, extremely hygroscopic $[\alpha]_D^{20.5} = +6.7°$ (c = 4.03% in water) (8,9) $[\alpha]_D^{20.5} = +8.1°$ (c = 3.5% in ethanol) (34) Most suitable solvent for crystallization of small quantities appears to be a mixture of isopropanol and acetone (8)
Muscarine iodide	150 (30)	Slightly hygroscopic Very soluble in water
Muscarine tetrachloroaurate	122–123 (8,9) 117.5–118 (1) 116–119 (34) 120–121 (30)	Sparingly soluble in cold water and cold ethanol
Muscarine Reineckate	181–182 (8,9) 177–179 (30)	Very sparingly soluble in water Easily soluble in acetone
Muscarine tetraphenylborate	172–173 (1) 174–175 (30)	Insoluble in water Easily soluble in acetone Soluble in boiling ethanol and methanol
Muscarine di-*p*-toluyl-D-hydrogen tartrate, $C_{29}H_{37}NO_{10}$·${}^1/_2H_2O$ (5,18)	166 (5) 151–152 (18)	Sparingly soluble in isopropanol
Acetylmuscarine chloride		Crystalline, very hygroscopic (9, 34)
Acetylmuscarine chloroplatinate	185–192 (34)	
p-Chlorobenzoylmuscarine tetrachloroaurate	163–165 (30)	
p-Iodobenzoylmuscarine tetrachloroaurate	163 (30)	

It is noteworthy that between 120 and 380 times greater yields of muscarine have been obtained from *Inocybe patouillardi* (Bres.), than from fly agaric (11; for the occurrence of muscarine in Mexican fly agaric see ref. 12).

The occurrence of muscarine has also been discovered (41) in: *Inocybe fasıigiata* (Fr. ex Sch.) Quél., 0.01% muscarine chloride; *I.*

umbrina (Bres.), 0.003% muscarine chloride; *I. rimosa*, 0.0003% muscarine chloride (the figures refer to the fresh fungus).

In *Amanita muscaria* muscarine content is greatest in the red headskin (41).

Muscarine has so far not been chemically detected in further fungal species. The various reports of its occurrence (see ref. 9, p. 1008) are based purely on pharmacological tests carried out on crude extracts.

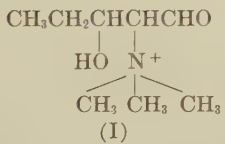
The solvent systems that have been used for paper chromatography are listed in Table II; suitable spraying reagents are listed in Table III; and some properties of the various salts and derivatives of natural muscarine are summarized in Table IV.

We now prefer solvent systems 4 and 7 (Table II) for paper chromatography, and additionally system 5 for column chromatography. The most suitable spraying reagents are Dragendorff's and bromocresol green. With regard to precipitants, it should be noted that although the Reineckate and tetraphenylborate are the most water-insoluble salts, they are at the same time nonspecific and therefore unsuitable for the isolation of pure muscarine from mixtures.

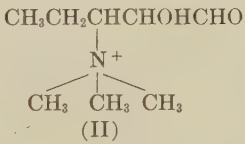
III. Structural Investigations of Muscarine

A. THE NITROGEN FUNCTION

When our degradative studies were begun on pure muscarine chloride, the currently accepted formulas were I and II. It is worth re-



(I)



(II)

membering that these were based by Kögl, Duisberg, and Erxleben (28) on a Hofmann degradation in which 23 mg. of (probably impure) muscarine base in aqueous solution was shaken in the cold for a few minutes with silver oxide. After filtration of the silver oxide and concentration of the solution, trimethylamine was isolated from the distillate (as the tetrachloroaurate in 38.5% yield) and a hydroxy-

valeric acid from the residue. By comparison with synthetic compounds this was assigned the structure of an α,β-dihydroxyvaleric acid.

This experiment pointed to a considerable alkali lability of muscarine. When it was repeated by us (8,9) and Kuehl *et al.* (34) under a variety of conditions, only negative results could be obtained. In no case could either trimethylamine or a dihydroxyvaleric acid be detected; on the contrary, only unchanged muscarine was recovered in most cases, which clearly argues its considerable stability to alkali.

Unfortunately our experiments were misinterpreted, it being implied that neither we nor Kuehl *et al.* were able to demonstrate the trimethylammonium group in muscarine (cf. ref. 30). However, this group could be demonstrated in the following way (8,9):

Pyrolysis of muscarine chloride, $(C_9H_{20}NO_2)^+Cl^-$, *in vacuo* at 200° led to normuscarine, $C_8H_{17}NO_2$ (oil, freely soluble in water and ether, b.p. 80–85°/0.1 mm., bulb tube) with elimination of methyl chloride. The fact that this could be quantitatively quaternized back to muscarine demonstrated that no further structural alterations could have resulted from the pyrolysis. *N*-Alkyl determinations showed in the case of muscarine three, and in the case of normuscarine only two, *N*-methyl groups, thus proving the presence of a trimethylammonium group. Trimethylamine could be demonstrated preparatively in a potash fusion followed by sublimation of the hydrochloride and crystallization of the sparingly soluble Reineckate. The potash fusion afforded trimethylamine in admixture with other amines. It could be first not be identified by its smell, as this was obscured by a faintly basic "acetylenic" odor (8,9); cf. the observation of King (27, p. 1752).

The pyrolysis of muscarine hydroxide *in vacuo* took mainly an abnormal course, for normuscarine was formed with elimination of methanol. Trimethylamine could be demonstrated only under selected conditions (30; cf. also ref. 10, p. 1033).

B. THE OXYGEN FUNCTIONS

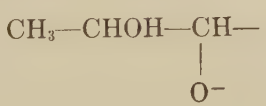
Muscarine shows no reducing properties (Tollens' reagent, Schiff, Fehling, Angeli-Rimini, triphenyltetrazolium chloride, etc. (8,9,34)). It is also unaffected by periodic acid (34). One oxygen atom is contained in a secondary hydroxyl function, for reaction with acetic anhydride afforded monoacetylmuscarine chloride and monoacetylnormuscarine (9,10,34), which no longer showed a hydroxyl band in

the infrared. That this was a secondary hydroxyl group followed from the oxidation of muscarine to a ketone (10,13).

The second oxygen atom could not be present as a carbonyl or amine oxide function, for the infrared spectrum did not exhibit a carbonyl band, nor could muscarine be reduced either catalytically or with metal hydrides. The molecule is therefore saturated. Taken in conjunction with the molecular formula, this means that muscarine must be monocyclic. It was tempting to assume the presence of a cyclic ether, since alkoxy groups could not be demonstrated analytically. The stability of the compound to reducing agents, acetolysis mixtures (acetic acid–acetic anhydride–sulfuric acid), and dilute mineral acids excluded a three- or four-membered ring (10). A tetrahydrofuran structure appeared to us most probable. Its location in the infrared spectrum by means of ether bands in the 9.1–9.3 μ region is, however, not an easy matter, as was clearly shown by comparison with a large number of model compounds. Certain proof of a tetrahydrofuran was furnished by Jellinek's X-ray analysis (26) and in our work by the infrared spectrum of muscarone (13) (using the characteristic carbonyl frequency of tetrahydrofuranones).

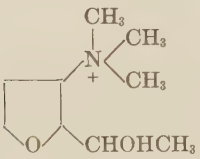
C. THE CARBON SKELETON

Oxidation with chromic acid, designed to test the presence of alkyl side chains (21), provided important results. Muscarine afforded only one mole of acetic acid and no trace of higher fatty acids. As soon, however, as muscarine was treated with phosphorus tribromide (ring fission) and the bromides so formed were reduced with zinc dust or lithium aluminum hydride, a large amount of propionic acid as well as traces of valeric acid could be detected in addition to acetic acid. This result could be interpreted as fission and partial reduction of a glycol monoether. Reduction with hydriodic acid and phosphorus (after Herzig-Meyer) pointed in the same direction, for in addition to methyl iodide (the major product), ethyl iodide was clearly detected. Oxidation of muscarine with hypoiodite gave small but significant amounts of iodoform. This led us erroneously to infer (10) the presence of the grouping

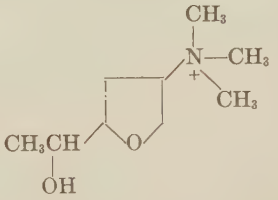


Micro potash fusion of muscarine had, as previously mentioned, resulted in methylamine as well as dimethylalkylamines, including distinct quantities of dimethylethylamine.

The interpretation of all the degradative evidence so far adduced, taken in conjunction with the stability of muscarine to acid, led us to propose structure III or IV for muscarine, the latter appearing to us



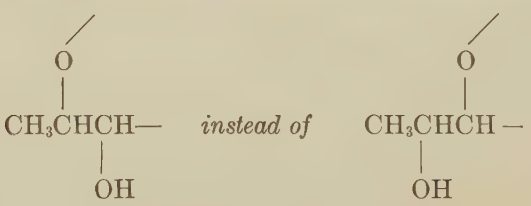
(III)



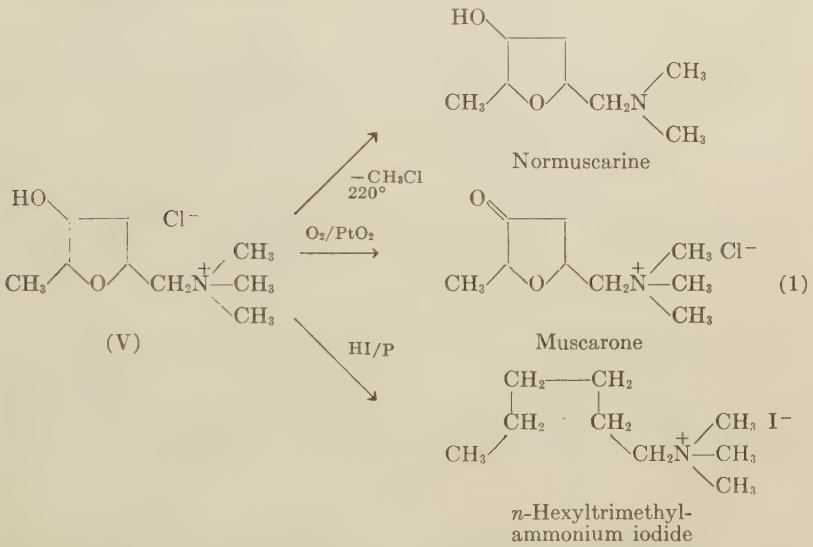
(IV)

the more probable. These structures certainly account for the tetrahydrofuran ring, the relative positions of O and N as in choline, the methyl side chain, the secondary hydroxyl group, and the glycol monoether grouping.

It must be emphasized that all the experiments described could be carried out only on milligram quantities because of the minute amounts of material available to us. Unfortunately, the crop of fly agaric harvested in Switzerland during 1955 was negligible, so that no further degradative work could be undertaken for a prolonged period. However, synthetic work carried out in the interim soon showed that formulas III and IV would have to be modified (13). Catalytic oxidation of muscarine chloride with platinum dioxide (PtO_2) in the presence of oxygen afforded muscarone (isolated as the tetrachloroaurate), whose carbonyl frequency in the infrared spectrum at 1754 cm.$^{-1}$ indicated the presence of a five-membered cyclic ketone. This observation thus necessitated attachment of the secondary hydroxyl group to the tetrahydrofuran ring. The corresponding ketone derived from IV showed a carbonyl band at 1709 cm.$^{-1}$. In consequence, the glycol monoether grouping had to be modified thus

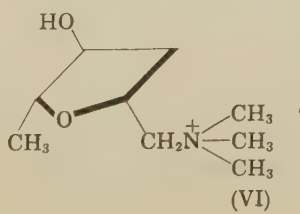


The carbon atom thus freed from the ring had to be inserted between the tetrahydrofuran ring and the trimethylammonium function, since another *C*-methyl group was not permissible. The stability of muscarone to alkali excluded α- or β-amino ketones, so that a consideration of previous arguments now led to V for muscarine. This still contained the same structural features as III and IV.



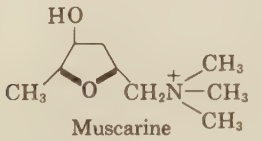
Meanwhile, Kögl and his collaborators (30) had been able, by an examination of the nonvolatile products from the Herzig-Meyer degradation, to isolate *n*-hexyltrimethylammonium iodide (compare the formation of valeric acid on chromic acid oxidation, mentioned above), a very important degradation product which contains all the carbon atoms of the muscarine molecule.

Final proof for structure V was provided by Jellinek's X-ray analysis (26,30), which also established the stereochemistry of the side chains as depicted in VI. Muscarine thus represents an entirely new structural type among alkaloids.

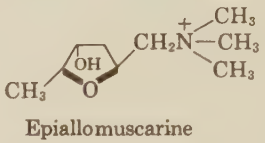


IV. Syntheses of Muscarine and Its Stereoisomers

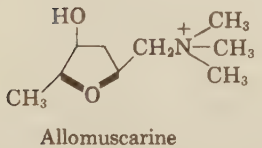
The three centers of asymmetry in the muscarine molecule limit the number of racemates to four. These are designated as follows, according to the convention of Hardegger, Eugster, and Kögl (cf. ref. 4):



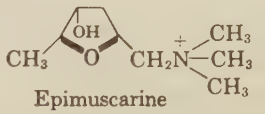
Muscarine



Epiallomuscarine

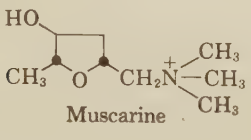


Allomuscarine

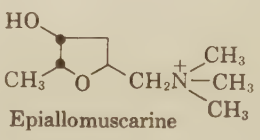


Epimuscarine

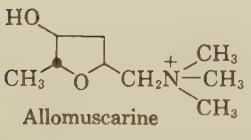
For the sake of simplicity, the following equivalent formulas are often used in the literature. (The heavy dot denotes a hydrogen atom lying above the molecular plane according to the convention of Linstead (35); carbon atom 2 always carries a heavy dot.)



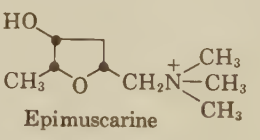
Muscarine



Epiallomuscarine



Allomuscarine



Epimuscarine

In epimuscarine and allomuscarine the hydroxyl group and basic side chain are on the same side of the annular plane, whereas in muscarine and epiallomuscarine they are on opposite sides. Epimuscarine thus differs from muscarine by an inversion of the hydroxyl group at C-3, allomuscarine by an inversion of the basic side chain at C-5, and epiallomuscarine by an inversion of both these groups.

As was to be expected, these stereochemical possibilities posed interesting problems of stereoselectivity in synthesis as well as in the complete separation of isomers and their configurational assignment.

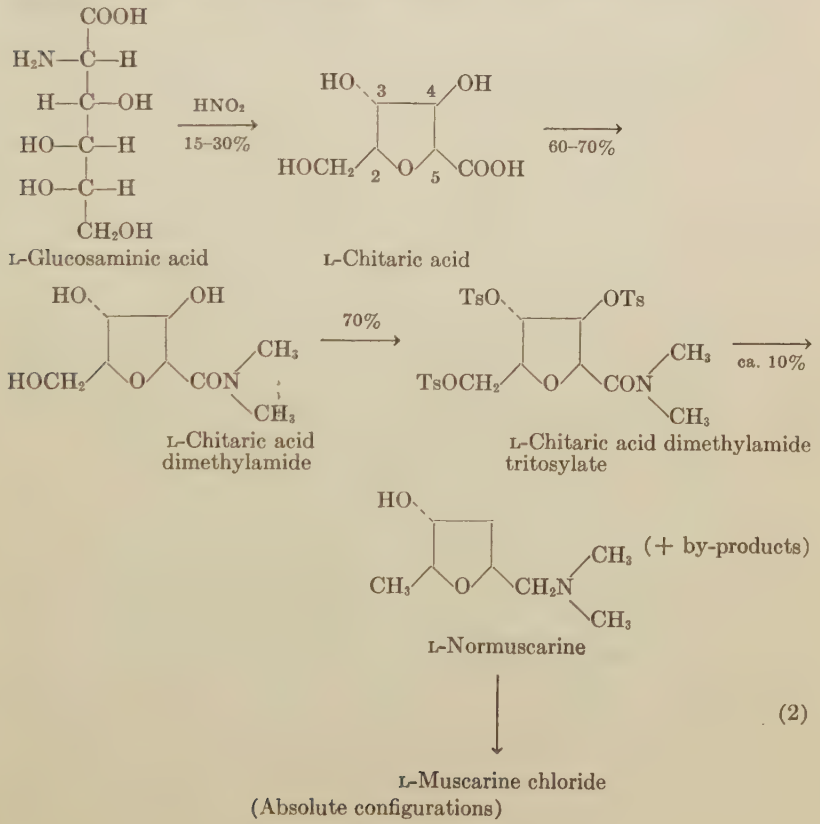
Furthermore, the marked stereospecificity of biological muscarine action which came to light constitutes an important pharmacological finding.

A. SYNTHESIS OF D- AND L-MUSCARINE FROM CHITARIC ACID (22,23,42)

(Equation 2)

Diazotization of glucosaminic acid affords L-chitaric acid, which, as transpired from this synthesis, has the same absolute configuration at carbon atoms 2, 3, and 5 as natural muscarine. L-Chitaric acid can be obtained in about 15–30% yield from L-glucosaminic acid, which is prepared from L-arabinose.

In this synthesis (see eq. 2), L-chitaric acid methyl ester, obtained by the action of diazomethane on L-chitaric acid, was con-



verted to the dimethylamide and then with *p*-toluenesulfonyl chloride to the tritosylate. This was reduced by means of lithium aluminum hydride in boiling tetrahydrofuran to a mixture of reduction products, including normuscarine. This could be purified by quaternization of the tertiary bases with methyl iodide and subsequent fractional crystallization of the tetraphenylborates. Decomposition of this salt and conversion to the chloride afforded, on repeated crystallization, pure L-muscarine chloride (same configuration as natural muscarine).

Lithium aluminum hydride thus fulfills three functions simultaneously: reductive fission of the primary and one secondary tosyloxy group (at C-4 of the tetrahydrofuran ring), elimination of the tosyl group at C-3, and reduction of the acid amide to the tertiary amine. The yield of the desired product was small, since in part the wrong oxygen function was either eliminated (C-3) or retained (C-4). Modification of this procedure (for instance, by way of the iodide obtained by reaction of the primary tosyloxy group with sodium iodide in acetone and a two-step reduction with Raney nickel and lithium aluminum hydride) did not lead to improved yields.

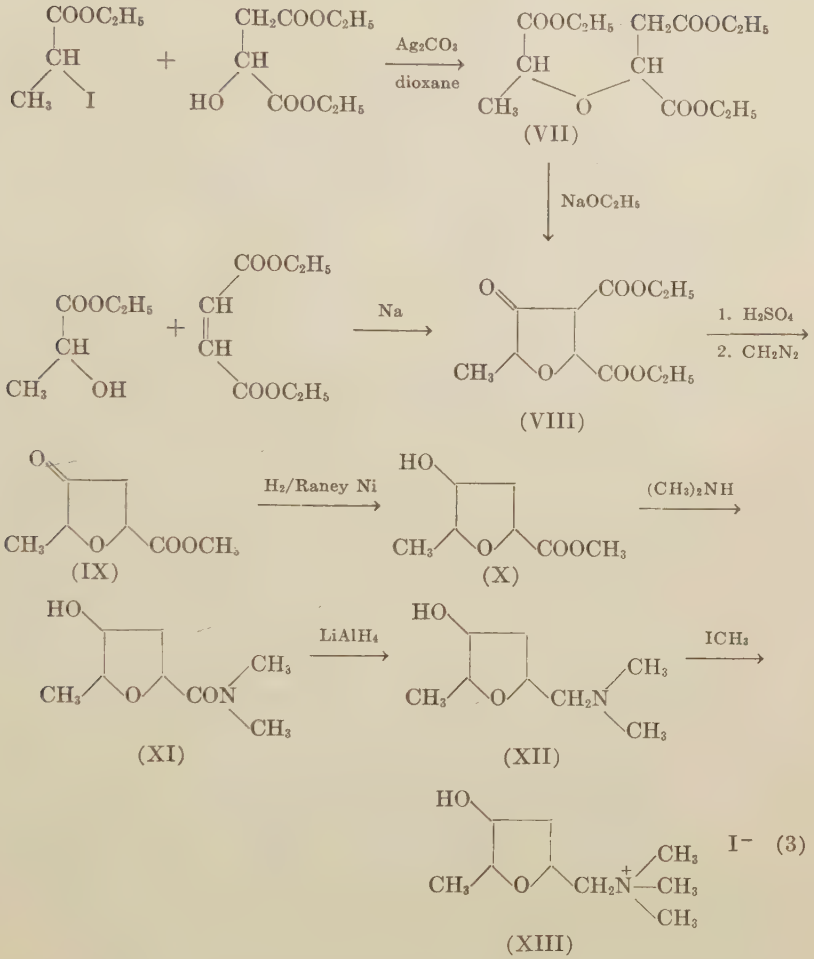
The unnatural D-muscarine was similarly synthesized from D-glucosamine via D-chitaric acid.

The value of these elegant syntheses lies not in their preparative use, for they do not make muscarine easily accessible, but in the fact that they unequivocally establish its absolute configuration.

D-3-Desoxyallosaminic acid can be used in place of glucosaminic acid as starting material in this muscarine synthesis. Lithium aluminum hydride reduction in the last step then affords substantially better yields of normuscarine than in the procedure using chitaric acid (42).

B. SYNTHESIS VIA TETRAHYDROFURANONES (3,4,44,45) (Equation 3)

When iodopropionic ester and malic ester are reacted in the presence of silver carbonate in boiling dioxane, there is obtained a tricarbethoxy ether (VII), which can be cyclized by a Dieckmann condensation to 2-methyl-4,5-dicarbethoxytetrahydrofuran-3-one (VIII). It is more convenient to condense the sodium salts of α-hydroxycarboxylic esters with maleic or fumaric ester (cf. ref. 6), to give the furanone (VIII) directly. On boiling with 10% sulfuric acid, 2-methyl-4,5-dicarbethoxytetrahydrofuran-3-one is hydrolyzed and



decarboxylated, affording the desired 2-methyltetrahydrofuran-3-one-5-carboxylic acid.

Several reactions have been carried out with this keto acid (see ref. 3), but only one has so far been described in detail (4); esterification with diazomethane afforded the methyl ester (IX), which was reduced with Raney nickel in methanol to X. This was then reacted with 33% dimethylamine solution in alcohol at 100° under pressure to give the dimethylamide (XI). Its reduction with lithium alumi-

num hydride in ether–dioxane gave the norbase (XII), which was converted to a series of crystalline salts.

The authors have modified their original claim to have prepared muscarine and its stereoisomers by this route (see summary in ref. 3) in a later communication (4), where they point out that in fact only little or no muscarine was obtained and that the isolated crystalline isomer had the allo configuration.

This statement merits the following observations:

1. A proof of configuration was announced but has not so far been published.

2. A comparison with the salts of allomuscarine of established structure and configuration (see Section IV-D) shows considerable discrepancies, so that the supposed "allomuscarine" of Kögl and collaborators probably does not possess the allo configuration.

3. A comparison with the other muscarine isomers, which have meanwhile become available, shows that Kögl's "allomuscarine" is probably not identical with any of them.

4. The recorded boiling points of the norbase and of 2-methyl-5-dimethylaminomethyltetrahydrofuran-3-one (allonormuscarone), as well as a number of other physical constants, are difficult to reconcile with the alleged structure.

Thus the configuration and constitution of the product obtained in this synthesis are still in doubt.

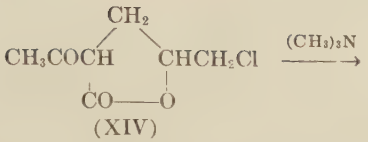
The following were synthesized in the same manner: desmethylmuscarine (*cis* and *trans* isomers) and desmethylmuscarone (44).

The following were synthesized via thiophanones: desmethylthiomuscarone, the two stereoisomeric desmethylthiomuscarines, thiomuscarone, thiomuscarine, and epithiomuscarine (45).

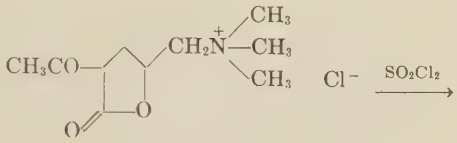
C. RING CLOSURE OF 1,4-DIOLS TO SUBSTITUTED TETRAHYDROFURANS (5,32,33)

(Equation 4)

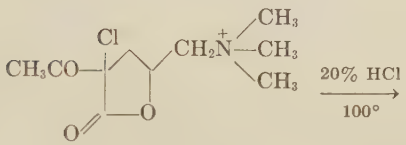
Condensation of epichlorhydrin with sodioacetoacetic ester smoothly affords α-acetyl-δ-chloro-γ-valerolactone (XIV), which could be reacted in poor yield with trimethylamine in a sealed tube. Chlorination and subsequent hydrolysis with 20% hydrochloric acid (decarboxylation) gave 2-hydroxy-4-chloro-5-oxohexyltrimethylammonium chloride (XVII). Hydrolysis of the halogen function with silver acetate or calcium carbonate gave the ketodiol (XVIII), whose keto group could be reduced to the alcohol either with sodium boro-



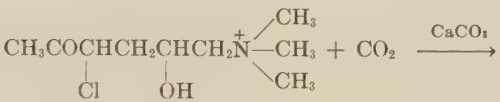
(XIV)



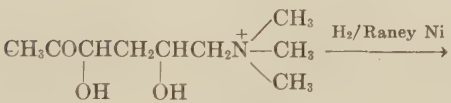
(XV)



(XVI)

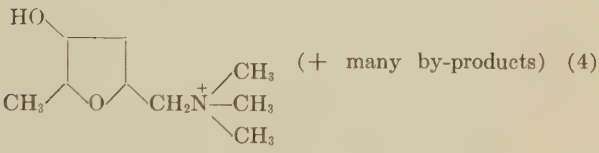


(XVII)



(XVIII)

(XIX)



(XX)

hydride or Raney nickel. Ring closure to the tetrahydrofuran derivative (XX) was achieved with concentrated sulfuric acid.

The intermediates (XVII, XVIII, and XIX) and the end product (XX) were sirupy and presumably represented mixtures of stereo-

isomers and foreign products. On the basis of biological experiments the authors assumed the end product to contain a considerable quantity of *d,l*-muscarine. Attempts at purification over cellulose columns (see ref. 5), however, revealed the presence of a number of structurally different impurities. Neither muscarine nor any of its stereoisomers has apparently been isolated in pure condition so far from this reaction sequence. The only crystalline tetrachloroaurate had too low a melting point (69–72°, 85–86°, instead of 93–94°).

The published account of this synthesis is not altogether convincing.

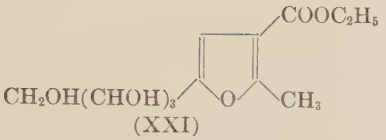
A preliminary announcement has appeared of a synthesis of muscarine isomers by ring closure of a 1,4-bromohydrin (43).

D. SYNTHESIS OF ALL MUSCARINE ISOMERS FROM FURAN DERIVATIVES (14–18)
(Equation 5)

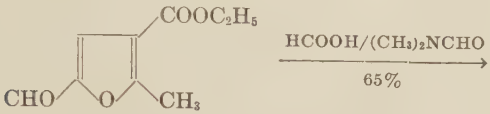
The key substance in this synthesis is 2,3-dihydro-2-methyl-5-dimethylaminomethylfuran-3-one (XXVIII). Its reduction with a variety of reducing agents and the development of a preparatively useful method of separation made possible the synthesis of all four muscarine isomers as well as muscarone and allomuscarone.

The dihydrofuranone (XXVIII) was prepared by the following sequence of reactions from glucose and acetoacetic ester via the known 2-methyl-5-tetrahydroxybutylfuran-3-carboxylic ester (XXI) and 2-methyl-5-formylfuran-3-carboxylic ester (XXII). Reaction of the aldehyde with dimethylformamide–formic acid introduced the desired basic side chain. The ester group at C-3 was then subjected to a Curtius degradation. Acid hydrolysis of the benzylurethane (XXVI) led, with elimination of benzyl alcohol, carbon dioxide, and ammonia, directly to the dihydrofuranone (XXVIII). It was subsequently found that the azide could be directly hydrolyzed to the dihydrofuranone. The reaction presumably proceeds via the (not isolated) imine (XXVII). This represents a new, not previously published route to "β-furanols." Alkaline hydrolysis of XXVI resulted in complete destruction of the furan ring.

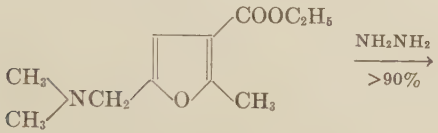
The dihydrofuranone (XXVIII) is a pale yellow oil (b.p. 46–49°/0.001 mm.) which is very sensitive to oxidation. Its constitution was established from, among other data, its very characteristic infra-



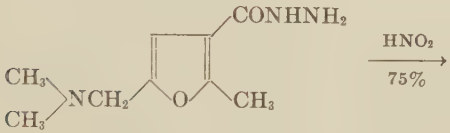
(XXI)



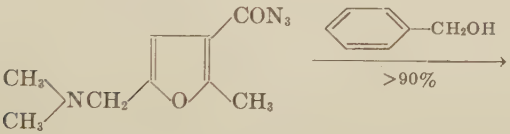
(XXII)



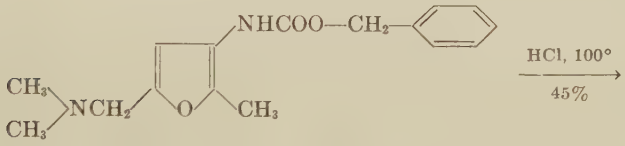
(XXIII)



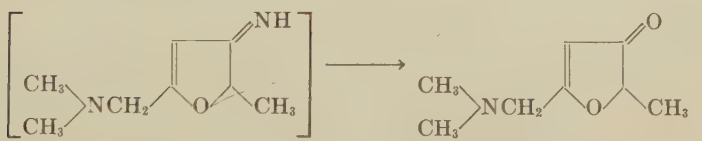
(XXIV)



(XXV)



(XXVI)



(XXVII) (XXVIII) (5)

red and ultraviolet spectra (λ_{max}(MeOH) 261 mμ, ϵ_{max} 10,300), as well as from the course of the reductions to which it was subjected. These were performed with a variety of reducing agents and led to the following results (see eqs. 6 and 7).

1. Reduction of the dihydrofuranone (XXVIII) with *alkali borohydrides*, particularly potassium borohydride in aqueous methanol, led, with reduction of the carbonyl group and the ethylenic double bond, to a mixture of stereoisomeric norbases. The composition of this mixture varied widely with reaction conditions. The best yields of normuscarine were obtained when a strong water-soluble tertiary base like triethylamine was added to the reaction. In addition to normuscarine, substantial amounts of epinormuscarine were always obtained. The formation of by-products and fission products could not be avoided, as might be expected from the sensitivity of the ketone (XXVIII).

2. When the dihydrofuranone (XXVIII) was reduced catalytically with *Raney nickel* in dilute aqueous sodium hydroxide, practically pure epinormuscarine was obtained.

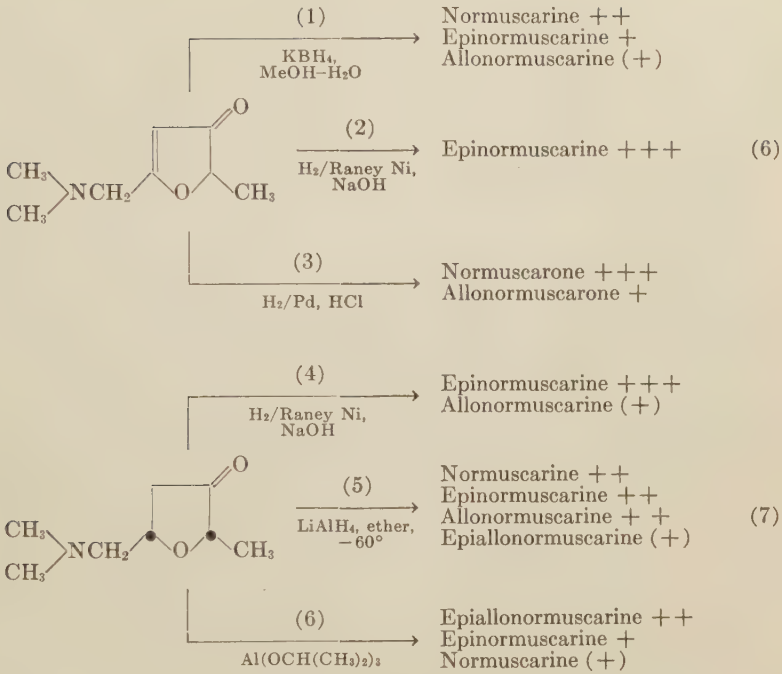
3. *Palladium* (10% on charcoal) in dilute hydrochloric acid, on the other hand, reduced only the ethylenic double bond to yield normuscarone in major amount, together with a little allonormuscarone.

4. When normuscarone was reduced with Raney nickel in aqueous sodium hydroxide, almost pure epinormuscarine was formed. Allonormuscarine could occasionally be detected in small amounts in the infrared spectrum.

5. Reduction of normuscarone with lithium aluminum hydride in ether at low temperatures led to a sterically nonuniform product consisting of approximately equal amounts of normuscarine, epinormuscarine, and allonormuscarine. This method is nevertheless useful, since both the latter compounds can be readily separated from normuscarine by simple distillation. Epiallonormuscarine could be detected occasionally in small amounts.

6. The missing fourth isomer, epiallonormuscarine, became accessible for the first time by *Meerwein-Ponndorf reduction* of normuscarone, which also afforded considerable amounts of epinormuscarine which could, however, be readily separated by distillation. Minor amounts of normuscarine were usually detectable.

The relative amounts of products, indicated in equations 6 and 7



by plus signs, represent only a qualitative estimate; quantitative estimation is made difficult by the formation of by-products.

The most easily accessible isomer by the methods outlined is epimuscarine; the most difficult so far, epiallomuscarine.

The yields were not good at all stages particularly as special attention was given to the purity of the products isolated.

Separation of the Isomeric Norbases. A large number of experiments designed to prepare the pure quaternary salts from the reaction mixtures were, in most cases, relatively unsuccessful. An exception was epinormuscarine, obtained practically free of isomers by reduction of the dihydrofuranone (XXVIII) with Raney nickel. In other cases, however, even partition chromatography over very large cellulose columns (e.g., substance/cellulose ratio, 1:1000 and greater) did not result in any appreciable separation, the R_f values of the components being far too similar. (This, incidentally, also applies to the solvent system proposed by Kögl (30).)

Some separation was achieved by fractional crystallization of the very readily crystallizable tetraphenylborates, for muscarine tetraphenylborate accumulated in the head fractions. Similar enrichment also resulted from the chromatography of the tetraphenylborates over neutral aluminum oxide in acetone solution, and of the chlorides in isopropanol over acid aluminum oxide. But these and other procedures were abandoned when it became possible to separate the *tertiary norbases.*

A preliminary separation could be achieved by fractional distillation since the isomers which are intramolecularly hydrogen-bonded (epi and allo) boil at distinctly lower temperatures (30–50°/0.001–0.02 mm.) than the other two isomers (60–80°/0.001–0.02 mm.). Further separation and purification were attained by *adsorption chromatography.* We have used Al_2O_3 as adsorbent and benzene with increasing amounts of methanol or ether as eluent and followed the course of the separation by means of infrared spectra. In this way the subtle stereochemical differences and presence or absence of intramolecular hydrogen bonding could be utilized to effect a separation.

Epinormuscarine is eluted first from Al_2O_3, followed closely by allonormuscarine. Normuscarine and epiallonormuscarine appear much later. In the course of gas chromatographic separation epi- and allonormuscarine also travel through the column much more quickly than the other pair of isomers (19).

These results might be used to effect separation of the mixtures obtained in the syntheses described in Sections IV-B and IV-C.

During the reduction of the dihydrofuranone (XXVIII) with KBH_4, the 3,4-dehydronormuscarines were formed in small amount. They were separated by very careful chromatography over Al_2O_3, being eluted in the following order: epi-, allo-, *cis*-4,5-dehydro-, *trans*-4,5-dehydronormuscarines, normuscarine, epiallonormuscarine. Catalytic reduction of the two dehydronormuscarines affords stereospecifically epinormuscarine and normuscarine (46).

Configurational Proof of the Synthetic Muscarine Isomers. The configurations were determined with the aid of infrared spectra and an oxidative method. The infrared spectrum provides directly part of the stereochemistry since both isomers in which the hydroxyl and dimethylamino groups are *cis* oriented (epi and allo) show, because of intramolecular hydrogen bonding, a bonded (concentration-inde-

pendent) OH— stretching band at 3.16 μ, whereas normuscarine and epiallonormuscarine, in sufficiently dilute solution, both exhibit a free OH— stretching band at 2.77 μ.

The behavior of both norbases on distillation, adsorption chromatography, and gas chromatography is entirely in line with this. The relative positions of the CH_3— and —$CH_2N(CH_3)_2$ groups followed from catalytic oxidation with O_2/Pt (20). This afforded, in 60–80% yield, muscarone from muscarine and epimuscarine, on the one hand, and allomuscarone from allomuscarine and epiallomuscarine on the other. The identification was carried out by a comparison of infrared spectra of the tetraphenylborates and tetrachloroaurates with the corresponding derivatives of muscarone and allomuscarone obtained by the hydrogenation in acid solution with a palladium catalyst of the dihydrofuranone (XXVIII). There was complete identity between the muscarone obtained from natural muscarine and the synthetic muscarone preparations. The isomeric allomuscarone iodide showed, as expected, practically the same C=O frequency as muscarone iodide (1758 cm.$^{-1}$, potassium chloride disk). In the long wavelength region of its infrared spectrum and in its melting point (135–137°, muscarone iodide 162–164°) allomuscarone iodide was distinctly different.

The constitutional proof of the synthetic (±)-muscarine followed from a comparison of the infrared spectra of its iodide, chloride, and the norbase with the corresponding derivatives of natural muscarine. Although natural muscarine is optically active, whereas the synthetic preparation is a racemate, there was complete identity of spectra of the solid salts (even in the fingerprint region).

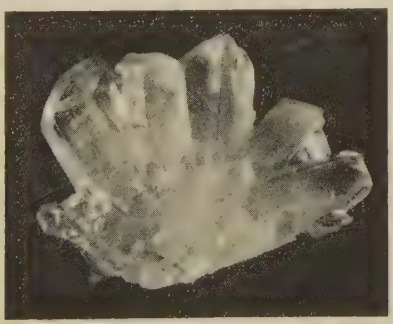


Fig. 2. Crystalline (±)-epimuscarine iodide.

The structure and configuration of the four isomers isolated are thus proved unambiguously. A summary of melting points of a number of salts is given in Table V. Crystalline epimuscarine chloride is shown in Figure 2, and the infrared spectra of the four isomeric chlorides are shown in Figure 3.

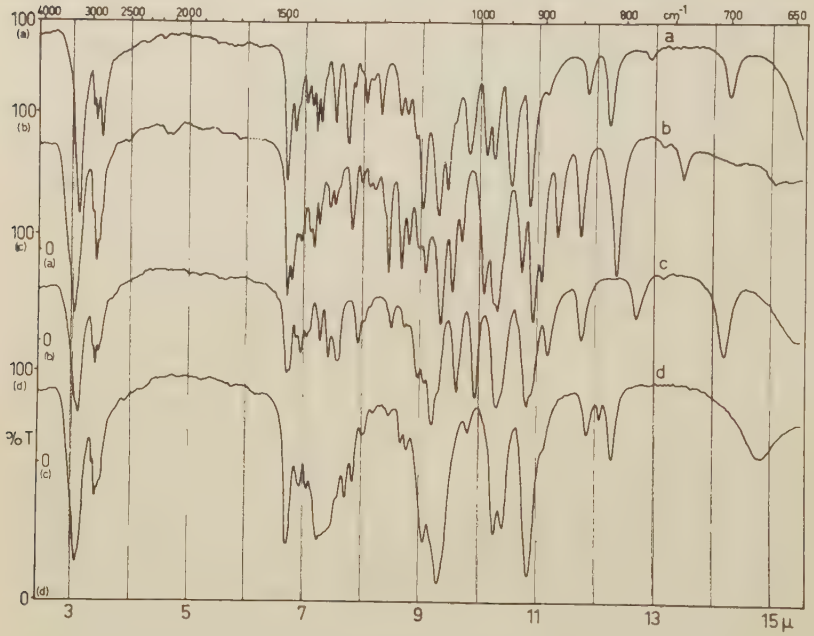


Fig. 3. Infrared spectra of the isomeric muscarine chlorides (by Dr. E. Girod, Basle). Spectrophotometer, Perkin-Elmer, Model 21, sodium chloride prism; resolution, 927; speed, 1 μ/min. All spectra in potassium bromide. (*a*) (±)-Muscarine chloride; (*b*) (±)-epiallomuscarine chloride; (*c*) (±)-epimuscarine chloride; (*d*) (±)-allomuscarine chloride.

It must be emphasized that identity and purity of the isomeric muscarines are not easily established. This is partly due to the fact that the isomeric chlorides or iodides appear to form mixed crystals with sharp melting points; the infrared spectra, moreover, of such mixed crystals cannot be additively constructed from the infrared spectra of their components.

TABLE V
Melting Points of Salts of Muscarine Isomers
(in degrees Centigrade)

	Iodide	Chloride	Tetra-chloro-aurate	Tetraphenyl borate
L(+)-Muscarine	149–149.5	181–182	122–123	174–175
(±)-Muscarine	108–109	147–148	93–94	173–174
(±)-Epimuscarine	130–131	139.5–140.5	106–107	180–181
(±)-Allomuscarine	131–132	153–154	77.5–79	175–176
(±)-Epiallomuscarine	159–160	159–161	97–99	191–192
(±)-Muscarone	162–164	—	87–91	189.5–190.5
(±)-Allomuscarone	135–137	—	98–100	194–195

F. RESOLUTION OF RACEMIC MUSCARINE CHLORIDE INTO ITS ANTIPODES (5,18)

The resolution could be accomplished by repeated crystallization of the di-*p*-toluylhydrogentartrates from isopropanol and reconversion to the chlorides. When (−)-di-*p*-toluyl-D-tartaric acid was used as resolving agent, the less soluble salt of m.p. 151–152° furnished, on conversion to the chloride, the unnatural (−)-muscarine chloride (m.p. 179–180°, $[\alpha]_D$ − 8.4° in ethanol). Similarly, resolution with (+)-di-*p*-toluyl-L-tartaric acid afforded, from the less soluble salt (m.p. 151.5–152°), (+)-muscarine chloride, which is identical with natural muscarine chloride in every respect (rotation, melting point, biological activity). (−)-Muscarine chloride, on the other hand, shows less than 5% of the activity when estimated by its effect on blood pressure in the cat.

Kögl's claim that resolution of a sirupy (±)-muscarine chloride by means of (−)-di-*p*-toluyl-D-tartrate yielded "natural" muscarine is almost certainly incorrect. The authors recorded no rotation.

References

1. Balenović, K., D. Cerar, B. Gašpert, and T. Galijan, *Arhiv. kem.* (*Croat. Chem. Acta*), *27*, 107 (1955).
2. Bregoff, H. M., E. Roberts, and C. C. Delwiche, *J. Biol. Chem.*, *205*, 565 (1953).
3. Corrodi, H., E. Hardegger, F. Kögl, and P. Zeller, *Experientia*, *13*, 138 (1957).
4. Corrodi, H., E. Hardegger, and F. Kögl, *Helv. Chim. Acta*, *40*, 2454 (1957).
5. Cox, H. C., E. Hardegger, F. Kögl, P. Liechti, F. Lohse, and C. A. Salemink, *Helv. Chim. Acta*, *41*, 229 (1958).

6. Davis, M., and W. Bradley, Brit. Pat., 568,402 (1945); *Chem. Abstr., 41*, 3821 (1947).
7. Dudley, H. W., *Biochem. J., 23*, 1071 (1929).
8. Eugster, C. H., and P. G. Waser, *Experientia, 10*, 298 (1954).
9. Eugster, C. H., *Helv. Chim. Acta, 39*, 1002 (1956).
10. Eugster, C. H., *Helv. Chim. Acta, 39*, 1023 (1956).
11. Eugster, C. H., *Helv. Chim. Acta, 40*, 886 (1957).
12. Eugster, C. H., and G. Müller, *Helv. Chim. Acta, 42*, 1189 (1959).
13. Eugster, C. H., and P. G. Waser, *Helv. Chim. Acta, 40*, 888 (1957).
14. Eugster, C. H., *Helv. Chim. Acta, 40*, 2462 (1957).
15. Eugster, C. H., F. Häfliger, R. Denss, and E. Girod, *Helv. Chim. Acta, 41*, 205 (1958).
16. Eugster, C. H., F. Häfliger, R. Denss, and E. Girod, *Helv. Chim. Acta, 41*, 583 (1958).
17. Eugster, C. H., F. Häfliger, R. Denss, and E. Girod, *Helv. Chim. Acta, 41*, 705 (1958).
18. Eugster, C. H., F. Häfliger, R. Denss, and E. Girod, *Helv. Chim. Acta, 41*, 886 (1958).
19. Eugster, C. H., Unpublished experiments, 1958.
20. Eugster, C. H., *Helv. Chim. Acta, 40*, 905 (1957); Method of R.P.A. Sneeden and R. B. Turner, *J. Am. Chem. Soc., 77*, 190 (1955).
21. After the method of Garbers, C. F., H. Schmid, and P. Karrer, *Helv. Chim. Acta, 37*, 1336 (1954), modified by J. H. Lister, C. H. Eugster, and P. Karrer, *Helv. Chim. Acta, 38*, 221 (1955).
22. Hardegger, E., and F. Lohse, *Helv. Chim. Acta, 40*, 2383 (1957).
23. Hardegger, E., P. Liechti, F. Lohse, *et al.*, *Helv. Chim. Acta, 41*, 229 (1958).
24. Harnack, E., *Arch. exptl. Pathol. Pharmakol., 4*, 168 (1875).
25. Honda, J., *Arch. exptl. Pathol. Pharmakol., 65*, 454 (1911).
26. Jellinek, F., *Acta Cryst., 10*, 277 (1957).
27. King, H., *J. Chem. Soc. (London), 1922*, 1743.
28. Kögl, F., H. Duisberg, and H. Erxleben, *Ann., 489*, 156 (1931).
29. Kögl, F., H. Veldstra, and P. J. van der Laan, *Ann., 552*, 1 (1942).
30. Kögl, F., C. A. Salemink, H. Schouten, and F. Jellinek, *Rec. trav. chim., 76*, 109 (1957).
31. Kögl, F., C. A. Salemink, H. Schouten, and F. Jellinek, *Rec. trav. chim., 76*, 112 (1957).
32. Kögl, F., H. C. Cox, and C. A. Salemink, *Experientia, 13*, 137 (1957).
33. Kögl, F., H. C. Cox, and C. A. Salemink, *Ann., 608*, 81 (1957).
34. Kuehl, F. A., N. Lebel, and J. W. Richter, *J. Am. Chem. Soc., 77*, 6663 (1955).
35. Linstead, R. P., *et al.*, *J. Am. Chem. Soc., 64*, 1985 (1942).
36. Nothnagel, G., *Ber., 26*, 801 (1893); *Arch. Pharm., 232*, 261 (1894).
37. Openshaw, H. T., and S. Wilkinson, Private communication, July, 1955.
38. Schmiedeberg, O., and R. Koppe, *Das Muscarin*, F. C. W. Vogel, Leipzig, 1869.
39. After the method of Straub, W., and H. Fühner, *Pflügers Archiv, 119*, 127 (1907); *Arch. exptl. Pathol. Pharmakol., 59*, 179 (1908).
40. Thies, H., and F. W. Reuther, *Naturwissenschaften, 1954*, 230.

41. Eugster, C. H., and G. Müller, *Helv. Chim. Acta, 42,* 1189 (1959).
42. Hardegger, E., H. Furter, and J. Kiss, *Helv. Chim. Acta, 41,* 2401 (1958).
43. Matsumoto, T., and H. Maekawa, *Angew. Chem., 70,* 507 (1958).
44. Eugster, C. H., G. Zwicky, and P. G. Waser, *Helv. Chim. Acta, 42,* 1177 (1959).
45. Eugster, C. H., and K. Allner, unpublished results.
46. Eugster, C. H., R. Denss, E. Girod, and F. Häfliger, *Helv. Chim. Acta, 42,* 1191 (1959).

AUTHOR INDEX*

A

Abernethy, J. L., 252, *259*
Abraham, N. A., 18 (ref. 84a), *65*
Abraham, R. J., 307, *326*
Abramov, V. S., 236 (ref. 1), *255*
Adkins, H., 353, 354, *365*
Agett, A. W., 224 (ref. 2), 225 (ref. 2), 226, *255*, *259*
Agnello, E. J., 344, *364*
Ahrens, H. L., 130 (ref. 161), 158, 159 (ref. 161), *211*
Akabori, S., 354, *365*
Alder, K., 408 (ref. 328), 410 (ref. 1), *416*, *425*
Aldrich, P. E., 323 (ref. 115), *328*, 394 (ref. 273), *424*
Alkema, H. J., 183 (ref. 192), 186 (ref. 192), *212*
Allen, C. F. H., 360, *366*
Allen, R. J. P., 236 (ref. 3), *255*
Aller, B. V., 252, *255*
Allner, K., 442 (ref. 45), 444 (ref. 45), *455*
Allred, A. L., 279, 280 (ref. 12), *325*
Alphen, J. van, 217, 218, *256*
American Cyanamid Co., 93 (ref. 115), *115*
Amiard, G., 403 (ref. 276), 404 (refs. 274, 275), 405 (ref. 277), *424*
Amiel, Y., 317 (ref. 97), *327*
Anderson, D. H., 310 (refs. 62, 119), *326*, *328*
Anderson, R. C., 140, *211*
Anderson, W., 307, 308 (ref. 72), *327*
Andrew, E. R., 267, 275 (ref. 5a), 292 (refs. 5b, 5c), *325*
Andrews, L. J., 331 (ref. 13), *363*
Angeletti, E., 140 (ref. 43), 141 (refs. 43, 55), 142 (refs. 43, 55), 145 (ref. 43), 146 (ref. 43), 153 (ref. 43), 154 (ref. 43), 184 (ref. 43), 185 (ref. 43), *208*
Angus, H. F. J., 407 (ref. 304), *425*
Angyal, S. J., 347 (ref. 68), *364*
Anner, G., 135 (ref. 101), 137 (ref. 101), 159–163 (ref. 101), *209*
Apicella, M., 415 (ref. 281), *424*
Applequist, D. E., 387 (ref. 2), *416*
Appleyard, M. E. S., 372 (ref. 181), *421*
Ardis, A. E., 223, *256*
Ardizio, P., 121 (ref. 27), 123 (ref. 27), 127 (ref. 27), 131 (ref. 27), 159 (ref. 27), 161 (ref. 27), 163 (ref. 27), *207*, 247 (ref. 184), 248 (refs. 184, 185), *260*
Arens, J. F., 117–212
Arigoni, D., 377 (ref. 53), 382 (ref. 303), 395 (ref. 3), 397 (ref. 272), *418*, *424*, *425*
Arison, B. H., 317 (ref. 96), *327*
Armstrong, E. F., 350 (ref. 79), *365*
Arnold, J. T., 274 (ref. 4), 280 (ref. 4), *325*
Arnold, R. T., 341 (ref. 47), *364*
Arnold, W., 86, *115*
Arth, G. E., 135 (refs. 100a, 100b), 159 (refs. 100a, 100b), 160 (refs. 100a, 100b), *209*
Ashida, K., 350 (ref. 81), 354 (ref. 81), *365*
Asker, W., 414 (ref. 226), *422*
Aso, K., 100 (refs. 1, 2), *112*
Assony, S. J., 141 (refs. 51, 52), 142 (ref. 52), *208*
Atkinson, B., 355 (ref. 103), *365*
Auerhahn, A., 200 (ref. 153), *211*
Ausloos, P., 372 (ref. 313), *425*
Autrey, R. L., 405 (ref. 4), *416*
Awad, W. I., 376 (ref. 234), 385 (refs. 224, 230), 386 (ref. 234), *422*, *423*

B

Bachmann, W. E., 373 (refs. 5, 6), 374 (ref. 6), *416*

* Italic numbers refer to the bibliographies of the different papers.

Backer, H. J., 119, 142 (ref. 60), 144 (ref. 8), 149, 150 (ref. 8), 199, *207–209*, *211*
Badcock, W. E., 354 (ref. 96), *365*
Baddar, F. G., 401 (ref. 7), *416*
Baddeley, G., 337 (ref. 31), 348 (ref. 76), *363*, *365*
Bader, A. R., 241 (ref. 10), 254, *256*
Badger, G. M., 412 (ref. 8), *416*
Baganz, H., 144 (ref. 70), 149 (ref. 70), 150 (ref. 70), 190, *209*
Bagli, J. F., 403 (ref. 327), *425*
Bailey, P. S., 400 (ref. 160), *421*
Baker, V. B., 2 (ref. 45), *64*
Balandin, A. A., 329
Baldwin, F. H., 253 (ref. 23), *256*
Balenović, K., 432, 433 (ref. 1), 434 (ref. 1), *453*
Balint, A. E., 4 (refs. 70a, 70b), 10 (ref. 74), 38 (ref. 74), 41 (ref. 74), *64*, *65*
Ballard, S. A., 228 (ref. 80), 231 (ref. 123), *257*, *259*
Ballum, A. T., 350 (ref. 83), *365*
Bal'yan, Kh. V., 255 (ref. 11), *256*
Bamberger, E., 413 (ref. 9), *416*
Bamford, C. H., 381 (ref. 10), 414 (ref. 11), *416*
Bankert, R. A., 237 (ref. 88), 238 (ref. 89), 239 (refs. 87, 91), *258*
Barakan, M. Z., 383 (ref. 229), *423*
Baranger, P., 82 (ref. 82), *114*
Barber, M. S., 323 (ref. 114), *328*
Barclay, B. M., 339, *364*
Barnard, M., 377 (ref. 12), *416*
Barnes, H. M., 168 (ref. 128a), 180 (ref. 128a), *210*
Barnett, B., 226 (ref. 12), *256*
Barth, P., 84, *115*
Bartlett, P. D., 239 (ref. 13), *256*, 348 (ref. 77), *365*
Bartocha, B., 3 (ref. 1b), 13 (ref. 1a), *62*
Barton, D. H. R., 369, 382 (refs. 14, 303), 394 (refs. 13, 18–21, 240), 395 (refs. 15, 17, 299), 398 (ref. 17), 403 (ref. 21), 405 (ref. 4), 406 (refs. 16, 22), 415 (ref. 20), *416*, *417*, *423*, *425*
Bataafsche Pet. Maat., 217 (ref. 14), 220 (ref. 15), *256*
Bauer, R. S., 319 (ref. 103), *328*
Bauer, S. H., 241 (ref. 35), *256*
Baum, K., 124, *211*
Bauman, R. A., 141 (ref. 47), *208*
Bawn, C. E. H., 414 (ref. 23), *417*
Beames, A. W., 331 (ref. 9), *363*
Becker, B., 79, 83, 107 (ref. 104), *115*
Becker, E., 409 (ref. 127), *420*
Becker, E. D., 280 (ref. 22), *325*
Beears, W. L., 197 (ref. 191), *212*, 237 (refs. 88, 93), 238 (refs. 16, 90), 239 (ref. 91), *256*, *258*
Behal, 22, *62*
Bell, I., 406 (ref. 91), *419*
Benary, E., 33, *62*
Benson, S. W., 372 (ref. 148), 381 (ref. 24), *417*, *420*
Bentley, R., 230 (ref. 17), *256*
Benzinger, H., 119, 144 (ref. 7), 149 (ref. 7), 150 (ref. 7), 190 (ref. 7), *207*
Beránek, J., 220 (ref. 225), 222 (refs. 226–228), *262*
Bereza, St., 396 (ref. 245), *423*
Bergmann, E., 345 (refs. 59–61), *364*, 373 (ref. 282), 375 (ref. 25), *417*, *424*
Bergmann, F., 345 (ref. 61), *364*, 373 (ref. 26), *417*
Bergmann, M., 218, *256*
Bergmann, W., 403 (ref. 27), *417*
Berlin, T., 345 (ref. 59), *364*
Bernard, P., 246 (ref. 243), *262*
Bernasconi, R., 382 (ref. 303), 406 (ref. 22), *417*, *425*
Bernstein, H. J., 267, 280, 296 (ref. 36), 302, 304 (ref. 37), 305, 306 (ref. 66), 307, 309 (ref. 19), 314 (refs. 66, 85), *325–328*, 389 (ref. 28), *417*
Berson, J. A., 219 (ref. 20), *256*, 374 (ref. 29), 412 (ref. 29), *417*
Bestian, H., 218 (ref. 21), *256*
Beute, A. E., 142 (ref. 60), *208*
Beyerstedt, F., 168 (ref. 128), *210*
Beyler, R. E., 135 (ref. 100a), 159 (ref. 100a), 160 (ref. 100a), *209*
Bidon, F., 26 (ref. 2), 56 (ref. 2), *62*

Biekert, E., 383 (ref. 57), 387 (ref. 57), *418*
Biemann, K., 380 (ref. 51b), *417*
Billeter, J. R. 135 (ref. 101), 137 (ref. 101), 159–163 (ref. 101), *209*, 374 (ref. 30), 382 (ref. 30), *417*
Bills, C. E., 403 (ref. 31), *417*
Binz, A., 413 (ref. 218), *422*
Birch, A. J., 130 (ref. 114), 159 (ref. 114), 161 (ref. 114), *210*
Bird, C. W., 396 (ref. 317), *425*
Blacet, F. E., 372 (refs. 32, 33), *417*
Blades, A. E., 219 (ref. 167), *260*
Blair, J. M., 407 (ref. 305), 415 (ref. 302), *425*
Blanchard, C. A., 241, *259*
Blau, N. F., 240 (ref. 22), *256*
Bloch, F., 265, 272, *326*
Bloembergen, N., 270 (ref. 45), *326*
Blomquist, A. T., 221 (ref. 24), 231, 253 (ref. 23), *256*, 315 (ref. 90), *327*
Bloom, B. M., 75 (ref. 102), 79, 83, 85, 86, *115*
Boatner, C., 2 (ref. 22), *63*
Boekelheide, V., 3 (ref. 2a), *62*, 368 (ref. 165), *421*
Boer, T. de, 123 (ref. 162), 125 (ref. 162), 202 (ref. 162), *211*
Boese, A. B., 215, 219 (ref. 26), 233, 236 (refs. 29, 33), 237 (ref. 31), 240–242 (ref. 26), 249, 250, 253–255, *256*
Bogert, M. T., 374 (ref. 34), 378 (ref. 34), *417*
Bohlmann, F., 130 (ref. 161), 131 (ref. 167), 158, 159 (ref. 161), 200, *211*, 400 (ref. 130), 414 (ref. 96), *419*, *420*
Bohlmann, M., 414 (ref. 96), *419*
Bolstad, A. N., 217 (ref. 70), *257*
Bonne, B., 280 (ref. 18), 291 (ref. 18), *325*
Bonnema, J., 121 (ref. 20), 140 (ref. 20), 141 (ref. 20), 146 (ref. 20), 147 (refs. 20, 198), 148 (ref. 20), 155 (ref. 20), 156 (refs. 20, 198), 159 (ref. 20), 161 (ref. 20), 163 (ref. 20), 184 (ref. 20), 186–188 (ref. 20), *207*, *212*
Bonner, W. A., 338 (ref. 35), *363*
Bonnett, R., 340 (ref. 41), *364*
Boonstra, H. J., 121 (ref. 176), 140 (ref. 182), 141 (ref. 182), 143 (ref. 176), 144 (ref. 176), 145 (ref. 182), 146 (refs. 176, 182), 147 (refs. 176, 182), 151 (refs. 176, 182), 154 (ref. 176), 155 (ref. 176), 157 (ref. 176), 159 (ref. 176), 161 (ref. 176), 164 (ref. 182), 165 (ref. 176), 184 (ref. 182), 186 (ref. 182), *212*
Borgeaud, P., 414 (ref. 288), *424*
Borisov, A. E., 35 (ref. 46a), *64*
Bos, H. J. T., 120 (ref. 180), 121 (ref. 180), 161 (ref. 180), 176 (ref. 180), 177 (ref. 180), 191 (ref. 181), *212*
Boss, E., 78, *113*
Bosshard, H., 395 (ref. 3), 396 (ref. 100), *416*, *419*
Bothner-By, A. A., 275 (ref. 6), 276, 277 (ref. 7), 279–281, 284, 285, 286 (refs. 13, 14), 287, 291, 307, 309 (ref. 71), *325–327*
Bots, J. P. L., 374 (ref. 35), 382 (ref. 35), *417*
Bottini, A. T., 312, *327*
Boudakian, M. M., 119 (ref. 5), 140 (ref. 5), 141 (refs. 5, 61, 63), 142 (ref. 5), 143 (ref. 5), 144, 145–147 (ref. 5), 151 (ref. 5), 153 (ref. 5) 185 (refs. 5, 73), *207–209*
Bouman, J. G., 182 (ref. 138), *211*
Bowen, E. J., 371 (ref. 37), 375 (ref. 36), 414 (ref. 38), *417*
Boyer, J. H., 234 (ref. 34), *256*
Brack, H., 130 (ref. 93), 159 (ref. 93), *209*
Bradley, W., 442 (ref. 6), *454*
Brady, O. L., 402 (ref. 39), *417*
Brähler, B., 336 (ref. 25), *363*
Brandon, R. L., 399 (ref. 112), *419*
Brandsma, L., 140 (ref. 182), 141 (ref. 182), 145 (ref. 182), 146 (ref. 182), 147 (ref. 182), 151 (ref. 182), 164 (ref. 182), 184 (ref. 182), 186 (ref. 182), *212*
Braude, E. A., 1, 2 (refs. 3–7), 3 (refs. 3, 8), 8 (refs. 3, 7, 9, 9a), 30 (ref. 9).

35, *62*, 131 (ref. 115), 159 (ref. 115), 160 (ref. 115) 161 (ref. 115), *210*, 330 (ref. 1), 331 (refs. 7–10, 12), 332 (refs. 7, 12), 333 (ref. 27), 335 (ref. 10), 336 (ref. 27), 337 (ref. 10), 338 (refs. 10, 16), 340 (ref. 39), 342 (ref. 53), 345 (ref. 63), 348, 350 (refs. 84–87), 351, 354, *363–365*, 403 (ref. 40), *417*
Braun, J., 13 (ref. 66b), *64*
Bregman, J., 241 (ref. 35), *256*
Bregoff, H. M., 433 (ref. 2), *453*
Bremer, K., 389 (ref. 248), *423*
Brenner, G., 323 (ref. 115), *328*, 394 (ref. 273), *424*
Bridge, N. K., 369 (ref. 41), *417*
Brinckman, F. E., 13 (ref. 1a), *62*
Brintzinger, H., 141 (refs. 49, 50), *208*
Brockmann, H., 414 (ref. 42), *417*
Brode, W. R., 400 (refs. 43, 44), 402 (refs. 45, 314), *417*, *425*
Broekema, R., 165 (ref. 122), 169 (ref. 122), 171 (ref. 122), 191 (ref. 122), *210*
Brook, A. G., 333 (ref. 16), 338 (ref. 16), 360 (ref. 115), *363*, *366*
Brook, P. R., 283 (ref. 27), 317 (ref. 97), *325*, *327*
Brooks, B. T., 230, 231, *256*
Brooks, R. E., 223 (ref. 36), *256*
Brown, B. B., 410 (ref. 242), *423*
Brown, E., 374 (ref. 29), 412 (ref. 29), *417*
Brown, H. C., 160 (ref. 102), *210*, 332 (ref. 15), *363*
Brown, R. F., 343 (ref. 55), *364*
Bruckner, K., 404 (ref. 132), *420*
Bruderer, H., 395 (ref. 3), *416*
Brunet, V., 372 (ref. 46), *417*
Brutcher, F. V., Jr., 314 (ref. 84), *327*
Brutschy, F. J., 373 (ref. 290), *424*
Bryce-Smith, D., 407 (refs. 304, 305), 415 (ref. 302), *425*
Buchkremer, J., 230 (ref. 172), *260*
Buchschacher, P., 377 (refs. 53, 325), *418*, *425*
Buckles, R. E., 401 (ref. 54), *418*
Buckley, D., 334 (ref. 20), *363*
Büchi, G., 82 (ref. 85), *114*, 369, 379, 380 (refs. 49, 51a), 391 (ref. 50), 393 (ref. 48), 395 (ref. 3), 401 (ref. 52), 410 (ref. 52), *417*
Buisman, J. A. K., 403 (refs. 280, 284), 404 (refs. 200, 201), *422*, *424*
Buiter, F. A., 179 (ref. 194), *212*
Bullitt, O. H., 141 (ref. 47), *208*
Bullock, M. W., 106, *113*
Bullot, J., 27, *63*
Burg, W. J. van der, 137–139 (ref. 165), 163 (ref. 165), *211*
Burke, H. J., 317, *327*
Burnett, G. M., 414 (ref. 55), *418*
Burton, M., 371 (ref. 207), 400 (ref. 208), *422*
Busch, M., 16, *62*
Butenandt, A., 382 (ref. 56), 383 (ref. 57), 387 (ref. 57), *418*
Buttery, R. G., 412 (ref. 8), *416*
Butz, L. W., 334 (ref. 18), *363*
Buu-Hoï, Ng. Ph., 339, 342, *364*
Byrns, A. C., 255 (ref. 38), *256*

C

Calas, R., 387 (ref. 320), *425*
Caldwell, J. R., 217 (ref. 40), 224 (ref. 42), 226 (refs. 39, 41, 43, 44, 117), *256*, *258*
Caliezi, A., 131 (refs. 94, 96), 132 (ref. 90), 159 (refs. 90, 94, 96), 161 (refs. 90, 94), *209*
Calvert, J. G., 372 (ref. 32), *417*
Calvin, M., 241 (ref. 130), *259*, 412 (ref. 244), 414 (refs. 58, 243), *418*, *423*
Campbell, N., 339, *364*, 402 (ref. 59), *418*
Campos-Neves, A da S., 382 (ref. 14), *416*
Cantor, S. M., 217 (ref. 131), *259*
Carbide and Carbon Corp., 229 (ref. 45), *256*
Carlton, P. W., 359 (ref. 113), *366*
Caronna, G., 375 (ref. 184), *421*
Carroll, M. F., 21, *62*, 244–247, 254, *256*
Caserio, F. F. Jr., 321 (ref. 110), *328*
Castells, J., 404 (ref. 60), *418*

Cava, M. P., 102, 106, *112*, 409 (ref. 60a), *418*
Cerar, D., 432–434 (ref. 1), *453*
Cereghetti, M., 377 (ref. 325), *425*
Cerletti, A., 83 (ref. 97), *115*
Cerny, M., 35 (refs. 12, 12a), *62*, *63*
Cerrito, E., 231 (ref. 123), *259*
Chadwick, J., 337 (ref. 31), *363*
Chakrabarti, J. K., 323 (ref. 116), *328*
Chamberlain, N. F., 318 (ref. 99), *327*
Chang, F. T., 157 (ref. 113), *210*
Chapman, F. B., 347, *364*
Chapman, O. L., 399 (ref. 61), *418*
Chardonnens, L., 411 (ref. 62), *418*
Chase, G. O., 246–248 (refs. 154, 155), *259*
Chemical Abstracts, 119, *207*
Chick, F., 217, 220 (ref. 257), 222, 229, 240, 241 (ref. 258), 242, 248, 249 (ref. 259), 252, 253 (ref. 258), *262*
Chieffi, G., 374 (ref. 193), 379 (ref. 192), *422*
Chierici, L., 145, 147 (ref. 68), *208*
Chopard-dit-Jean, L. H., 248 (ref. 143), *259*
Christoph, F. J., 400 (ref. 117), *419*
Chute, W. J., 230 (ref. 49), *256*
Ciamician, G., 355, *365*, 368, 373 (refs. 63, 64, 71, 72, 74), 374 (ref. 73), 381 (refs. 68, 70, 76), 382 (refs. 68, 72, 76), 391 (ref. 69), 401 (ref. 66), 402 (ref. 67), 412, *418*
Ciusa, R., 402 (ref. 77), *418*
Civera, M., 390 (ref. 118), *419*
Clar, E., 331, 334 (refs. 5, 19), 344 (ref. 58), *363*, *364*, 400 (ref. 79), 414 (ref. 78), *418*
Clauson-Kaas, N., 67–70, 71 (refs. 7, 17, 20, 22, 27, 31, 47, 48, 87, 89), 72 (refs. 17, 20, 21, 31, 32, 91), 74 (refs. 7, 12, 20, 23, 31, 46, 87–89), 75, 76 (refs. 10, 91), 77 (ref. 91), 78, 82 (ref. 19), 84, 86 (ref. 25), 90 (ref. 17), 91 (ref. 17), 92 (refs. 17, 48), 93, 94 (refs. 14, 28), 95 (refs. 89, 90), 96 (refs. 89, 90), 97 (refs. 29, 89), 98 (ref. 49), 99 (ref. 11a), 100 (refs. 46, 48), 101 (refs. 31, 46, 87), 102 (refs. 12, 31, 46), 103 (refs. 5, 28), 104 (refs. 6, 23, 44), 105 (refs. 23, 44), 106 (refs. 13, 45), 107 (ref. 27), 110 (refs. 21, 23), 111 (ref. 44), *112–114*
Clemo, G. R., 130 (ref. 92), 131 (ref. 92), 159 (ref. 92), 160 (ref. 92), *209*
Cley, J., 171 (ref. 179), *212*
Clower, E. H., 220 (ref. 50), *257*
Coats, F. H., 140, *211*
Cochran, P. B., 218 (ref. 132), *259*
Cocker, W., 395 (ref. 80), *418*
Coenen, M., 232 (ref. 51), 255 (ref. 51), *257*
Cohen, A. D., 280 (ref. 21), 309 (ref. 59), *325*, *326*
Cohen, L. A., 314 (ref. 86), *327*
Cohen, W. D., 373 (ref. 81), *418*
Coleman, G. H., 219 (ref. 52), *257*
Coles, J. A., 2 (refs. 5–7), 3 (ref. 8), 8 (ref. 7), *62*
Coley, J. R., 329
Coll, 6 (ref. 86), *65*
Collins, C. J., 318 (ref. 100), *327*, 338 (ref. 35), 341 (ref. 47), *363*, *364*
Colonge, J., 24 (ref. 13), *63*, 246, *257*
Colthup, N. B., 151 (ref. 86), *209*
Conn, E. E., 356 (ref. 107), *366*
Conn, R. C., 249 (ref. 170), *260*
Connolly, E. E., 249, *260*
Conroy, H., 265–328
Constantin, J. M., 135 (ref. 100a), 159 (ref. 100a), 160 (ref. 100a), *209*
Cookson, R. C., 389 (ref. 84), 390 (ref. 84), 391 (ref. 82), 392 (ref. 83), 396 (ref. 317), *418*, *425*
Coombs, R. D., 2 (ref. 45), *64*
Coops, J., 230 (ref. 149), *259*
Cope, A. C., 242 (ref. 152), 245, 246, *259*, 316 (ref. 93), *327*
Corbier, B., 246 (ref. 243), *262*
Corey, E. J., 315 (ref. 87), 317, 322 (ref. 111), *327*, *328*, 377 (refs. 85, 86), *418*
Corrodi, H., 440 (ref. 4), 442 (refs. 3, 4), 443 (refs. 3, 4), 444 (refs. 3, 4), *453*
Cotton, F. A., 321 (ref. 109), *328*
Coulson, C. A., 298

Cox, E. F., 230 (ref. 218), *261*
Cox, H. C., 434 (ref. 5), 444 (refs. 5, 32, 33), 446 (ref. 5), 453 (ref. 5), *453*, *454*
Cramer, R., 118, 121 (refs. 3, 21), 122 (ref. 3), 123 (ref. 21), 126, 127 (refs. 3, 21), 129 (ref. 21), 130 (ref. 21), 153 (ref. 21), 154 (ref. 21), 156 (ref. 3), 157 (ref. 21), 163 (ref. 3), 164 (refs. 3, 21), 167 (ref. 3), 168 (ref. 3), 184 (ref. 3), 189 (ref. 3), 190, 198 (ref. 21), *206*, *207*
Crandall, J. L., 414 (ref. 170), *421*
Crauland, M., 123 (ref. 158), 125 (ref. 158), *211*
Creighton, A. M., 331 (ref. 11), 343 (ref. 11), *363*
Cremer, E., 329
Crisan, C., 16 (ref. 62), 24 (ref. 56), 27 (ref. 14), 39 (ref. 14), 55 (ref. 56), 57 (ref. 14), 58 (ref. 14), *63*, *64*
Cristol, S. J., 391 (ref. 87), *418*
Cross, B. E., 319 (ref. 104), *328*
Crouch, W. W., 217, 218 (ref. 53), *257*
Crowley, K., 395 (ref. 80), *418*
Croxall, W. J., 142 (ref. 57), *208*, 233 (ref. 55), *257*
Crump, J. W., 35 (ref. 12b), *63*
Crundwell, E., 391 (ref. 82), 392 (ref. 83), *418*
Cserr, R., 4 (refs. 70a, 70b), *64*
Cumming, W. M., 412 (ref. 88), *419*
Cuneo, J. F., 229 (ref. 68), *257*
Curphey, T., 380 (ref. 51a), *417*
Curtin, D. Y., 35 (ref. 12b), *63*
Cuvigny, Th., 9 (ref. 66a), 33 (ref. 14a), *63*, *64*
Cuza, N. W., 144 (ref. 76), *209*
Cretanovic, R. J., 329
Cziesla, M., 336 (ref. 25), *363*

D

Dahl, E., 380 (ref. 217), *422*
Dailey, B. P., 278, *325*
Dale, J., 402 (ref. 89), *419*
Daly, J. W., 314 (ref. 86), *327*
Dankova, T. F., 85, *115*
D'Ans, J., 216 (ref. 8), *256*
Darzens, G., 230 (ref. 56), *257*
Dashkewich, B. N., 220, 230, *257*
Dauben, W. G., 399 (ref. 307), 405 (ref. 90), 406 (ref. 91, 310), *419*, *425*
Davis, J. W., 353 (refs. 88–90), *365*
Davis, M., 442 (ref. 6), *454*
Davis, W., 369 (ref. 93), 372, *419*
Davison, B. K., 130 (ref. 92), 131 (ref. 92), 159 (ref. 92), 160 (ref. 92), *209*
Deakin, S., 221 (ref. 260), 222, *263*
Degering, E. F., 224, 225, 233 (ref. 65), *257*
Delacre, M., 2 (ref. 15), *63*
Deleo, E., 375 (ref. 184), *421*
Delwiche, C. C., 433 (ref. 2), *453*
Denss, R., 434 (ref. 18), 446 (refs. 15–18), 450 (ref. 46), 453 (ref. 18), *454*, *455*
Dessy, R. E., 13 (ref. 71a), *64*
Detroit, W. J., 336 (ref. 26), *363*
Dev, S., 315 (ref. 87), *327*, 410 (ref. 94), *419*
Dewar, M. J. S., 414 (ref. 11), *416*
Di, M., 355 (ref. 103), *365*
Diab, G., 123 (ref. 158), 125 (ref. 158), *211*
Dickert, Y. J., 216 (ref. 251), *262*
Dickey, J. B., 7 (ref. 21), *63*, 235 (ref. 67), *257*
Dickinson, W. C., 275 (ref. 23), *325*
Dien, C.-K., 104, *113*, 400 (ref. 160), *421*
Dietrich, P., 69 (ref. 88), 70 (ref. 22), 74 (refs. 12, 88), 102 (ref. 12), *112*, *114*
Diewald, J., 77, *114*
Dijkstra, R., 402 (ref. 139), 408 (ref. 137), 415 (ref. 138), *420*
Dilthey, W., 414 (ref. 95), *419*
Dimroth, K., 414 (ref. 96), *419*
Dimroth, O., 332 (ref. 14), *363*
Disselnkötter, H., 410 (ref. 168), *421*
Djerassi, C., 330 (ref. 3), 350 (ref. 82), *363*, *365*, 382 (ref. 303), *425*
Dobó, P., 84, *113*
Doering, W. v. E., 318, *327*, 410 (refs. 97, 98), *419*
Doornbos, T., 119 (ref. 6), 121 (ref. 20),

140 (refs. 6, 20), 141 (refs. 6, 20), 146 (refs. 6, 20), 147 (ref. 20), 148 (ref. 20), 155 (ref. 20), 156 (ref. 20), 159 (ref. 20), 161 (ref. 20), 163 (ref. 20), 169 (ref. 129), 171 (ref. 129), 184 (ref. 20), 186–188 (ref. 20), *207*, *210*
Dorfmann, L. M., 372 (ref. 182), *421*
Dorough, G. D., 414 (ref. 58), *418*
Dorp, D. A. van, 120, 121–123 (ref. 28), 127 (ref. 28), 130 (ref. 11), 132 (ref. 11), 133 (refs. 11, 12, 103, 104), 137–139 (ref. 165), 161 (refs. 11, 12, 103, 104), 162 (refs. 12, 103, 104), 163 (ref. 165), *207*, *210*, *211*
Dost, N., 336 (ref. 29), *363*, 414 (ref. 99), *419*
Doumani, T. F., 141 (ref. 67a), *208*, 229 (ref. 68), *257*
Dreiding, A. S., 35, *63*
Drenth, W., 127 (ref. 193), 128 (ref. 193), 146 (ref. 193), 164 (ref. 199), 169 (ref. 193), 196 (ref. 185), *212*
Dreux, J., 246, *257*
Drysdale, J. J., 313 (ref. 76), 314 (ref. 76), 319 (ref. 102), *327*, *328*
Dubb, H., 307 (ref. 68), *326*
Dudley, H. W., 429, 432, *454*
Duisberg, H., 428 (ref. 28), 429 (ref. 28), 435, *454*
Dull, M. F., 216 (ref. 133), 253 (ref. 32), *256*, *259*
Dunbar, R. E., 216 (ref. 71), 217 (ref. 70), *257*
Dunlop, A. P., 68 (ref. 34), 99 (ref. 35), 100 (ref. 36), 103, *113*, *115*
Dunn, F. P., 402 (ref. 39), *417*
Dutler, H., 396 (ref. 100), 397 (ref. 272), *419*, *424*
Dworkowitsch, P., 118, *206*

E

Eastman, R. H., 395 (ref. 285), *424*
Eberhardt, H-D., 409 (ref. 260), *423*
Ebnöther, A., 83 (ref. 107), *115*
Eckert, A., 414 (refs. 101, 169), *419*, *421*
Edward, J. T., 395 (ref. 80), *418*
Edwards, O. E., 224 (ref. 134), 225 (ref. 134), *259*
Efros, L. S., 219 (ref. 206), *261*
Eglinton, G., 120 (ref. 17), 122, 127 (refs. 17, 33), 128 (ref. 17), 154 (refs. 17, 33), 164 (ref. 17), 169 (ref. 17), 171 (ref. 17), *207*
Eichenberger, K., 134 (ref. 89), 159 (ref. 89), 161 (refs. 89, 106), 162 (ref. 106), *209*, *210*
Eichmann, G. G., 246–248 (ref. 154), *259*
Einstein, A., 269, *326*
Eisner, U., 340 (ref. 42), *364*
Eistert, B., 196 (ref. 147), *211*
Eiszner, J. R., 410 (ref. 269), *424*
El-Assal, L. S., 401 (ref. 7), *416*
Elderfield, R. C., 354 (ref. 100), *365*
Elgar, F., 413 (ref. 9), *416*
Ellinger, A., 106, *113*
Ellwanger, H., 141 (ref. 50), *208*
Elming, N., 67–115
Elton, G. A. H., 329
Elvidge, J. A., 320 (ref. 107), *328*, 347, *364*
Emerman, S. L., 82 (ref. 85), *114*
Emery, A. R., 216, *257*
Emmons, W. E., 412 (ref. 102), *419*
Engelhard, N., 232, *261*
Engelhardt, A., 347 (ref. 73), *365*
England, D. C., 353 (ref. 91), *365*
Eppstein, S. H., 356 (ref. 104a), *365*
Erdmann, D., 131 (ref. 110), 161 (ref. 110), *210*
Erdmann, H-M., 404 (ref. 133), *420*
Erickson, F. B., 220 (ref. 73), *257*
Erxleben, H., 428 (ref. 28), 429 (ref. 28), 435, *454*
Eschenbach, W., 220 (ref. 74), *257*
Eschenmoser, A., 27 (ref. 17), *63*, 130 (ref. 98), 159 (ref. 98), *209*
Esterle, J. G., 394 (ref. 103), *419*
Estes, R. R., 255 (ref. 75), *257*
Etienne, A., 387 (ref. 105), 403 (ref. 104), *419*
Eugster, C. H., 427–455
Evans, D. F., 276 (ref. 58), *326*
Evans, E. A., 8 (refs. 9, 9a), 30 (ref. 9), *62*

Eyring, H., 299 (ref. 70), *326*, 400 (ref. 113), *419*

F

Failer, G., 383 (ref. 57), 387 (ref. 57), *418*
Fakstrop, J., 68 (refs. 26, 51), 69 (refs. 18, 26, 51), 73, 74 (ref. 51), 80, *112*, *113*
Farben Akt.-Ges., I. G., 200 (ref. 153), *211*
Farrar, T. C., 310 (ref. 62), *326*
Fateen, A. K., 374 (ref. 235), *423*
Favorskiĭ, A. E., 121 (refs. 22–24), 123 (refs. 22, 23), 127 (refs. 22–24), 163 (ref. 24), 165 (ref. 24), 172 (ref. 24), *207*
Fawcett, J. S., 345 (ref. 63), *364*
Feitelson, B. N., 134 (ref. 95), 159 (ref. 95), *209*
Ferrier, G. S., 412 (ref. 88), *419*
Fessenden, R. W., 283, 304 (ref. 39), 309 (ref. 39), *325*, *326*
Feurer, M., 135 (ref. 100b), 159 (ref. 100b), 160 (ref. 100b), *209*
Ficini, J., 14 (ref. 18), 16 (ref. 18), 18 (ref. 19), 24 (ref. 58), 26 (ref. 65), 30 (ref. 19a), 37 (refs. 19, 65), 43 (ref. 18), 46 (ref. 18), 49 (ref. 19), 50 (ref. 19), 52 (ref. 65), 54 (ref. 58), *63*, *64*, 121 (refs. 29, 29a), 123 (refs. 29, 29a), 124 (ref. 29), 125, 128 (ref. 29), 164 (ref. 129), 168 (ref. 29), 169 (ref. 29), 171 (ref. 29), 180 (ref. 29), 184 (ref. 29), 195, 197 (ref. 29), *207*
Ficken, G. E., 340 (ref. 44), *364*
Fiedorik, F. T., 238 (refs. 76, 89), 239 (ref. 91), *257*, *258*
Field, E., 329
Fieser, L., 403 (ref. 106), *419*
Fieser, M., 403 (ref. 106), *419*
Findlay, S. P. 82 (ref. 52), 89, *113*
Fischer, E., 402 (refs. 107, 109), *419*
Fischer, F. G., 356
Fisher, G. T., 214 (ref. 77), *257*
Fisher, H. F., 356 (ref. 107), *366*
Fitzpatrick, J. T., 226 (ref. 265), 241 (ref. 78), *257*, *263*
Fodor, G., 82 (refs. 53–55a), 84, 86 (ref. 53), *113*
Folkers, K., 317 (ref. 96), *327*
Fonken, G. J., 405 (ref. 90), *419*
Forbes, E. J., 399 (refs. 108, 306), *419*, *425*
Ford, P. T., 241 (ref. 79), *257*
Forostyan, Y. N., 219, *262*
Foster, M. R., 275 (ref. 49), *326*
Fox, S. W., 106, *113*
Frankel, M., 402 (ref. 109), *419*
Franzen, V., 380 (ref. 217), *422*
Frederick, M. R., 238 (ref. 90), 239 (ref. 91), *258*
Frehden, O., 402 (ref. 296), *424*
Frei, Y., 402 (ref. 107), *419*
Freimiller, L. R., 142 (ref. 57), *208*
Frey, W., 216 (ref. 8), *256*
Fried, J., 358 (ref. 111), *366*
Friedlander, H. N., 369 (ref. 142), *420*
Friedrich, E. C., 387 (ref. 2), *416*
Friedrich, W.. 382 (ref. 56), *418*
Fries, D., 375 (ref. 323), 415 (ref. 323), *425*
Fromm, E., 119, 143, 144 (refs. 7, 71, 72), 149 (refs. 7, 71), 150 (refs. 7, 71, 72), 164 (ref. 71), 190, *207*, *209*
Frostick, F. C., 235 (ref. 175), *260*
Fühner, H., 429 (ref. 39), *454*
Fujisi, S., 375 (ref. 25), *417*
Fuller, G., 376 (ref. 110), *419*
Fulton, J. D., 401 (ref. 111), *419*
Furter, H., 87 (ref. 63a), *114*, 441 (ref. 42), 442 (ref. 42), *455*
Fuson, R. C., 141 (ref. 47), *208*

G

Gaede, J., 406 (ref. 289), *424*
Gaertner, R., 334 (ref. 17), *363*
Gaj, B. J., 9 (ref. 25), *63*
Gál, G., 82 (ref. 59), 110 (ref. 59), *113*
Galijan, T., 432–434 (ref. 1), *453*
Garbers, C. F., 437 (ref. 21), *454*
Gardner, P. D., 399 (ref. 112), *419*
Garven, F. C., 216 (ref. 71), *257*

Gašpert, B., 432–434 (ref. 1), *453*
Gaul, R. J., 316 (ref. 94), *327*
Genkin, E. I., 119 (ref. 10), *207*
Geux, W., 248 (ref. 143), *259*
Geyer, B. G., 228 (ref. 80), *257*
Gibbons, A. J., 11 (refs. 75, 76), 41 (ref. 75), *65*
Gilbert, W. W., 319 (ref. 102), *328*
Gillespie, R. J., 318 (ref. 101), *327*
Gillis, R. G., 141 (ref. 67), *208*
Gilman, H., 2, 7, 9, *63*, 230 (ref. 81), *257*
Gindy, M., 383 (ref. 122), 384 (ref. 122), 401 (ref. 7), *416*, *420*
Ginsburg, D., 79, *113*
Girling, P. M., 394 (ref. 103), *419*
Girod, E., 434 (ref. 18), 446 (refs. 15–18), 450 (ref. 46), 453 (ref. 18), *454*, *455*
Glasstone, S., 400 (ref. 113), *419*
Glavis, F. J., 233 (ref. 55), *257*
Glazier, E. R., 315 (ref. 87), *327*
Glens, K., 70 (ref. 27), 71 (ref. 27), 107 (ref. 27), *112*
Glick, R. E., 275 (ref. 6), 276, 277 (ref. 7), 279, 309 (ref. 71), *325*, *327*
Glos, M., 409 (ref. 260), *423*
Goddard, D. C., 356
Goffinet, B., 403 (ref. 276), 405 (ref. 277), *424*
Goheen, G. E., 219 (ref. 52), *257*
Gold, V., 216, *257*
Golden, J. H., 340 (ref. 43), *364*
Goldman, I. M., 391 (ref. 50), *417*
Gordon, A. S., 372 (ref. 167), *421*
Gorman, M., 350 (ref. 82), *365*
Gould, J. H., 402 (ref. 314), *425*
Graham, R. E., 242 (ref. 159), 243 (ref. 159), *259*
Graham, W., 133 (ref. 104), 161 (ref. 104), 162 (ref. 104), *210*
Grant, J. K., 358 (ref. 109), *366*
Greenberg, J., 217 (ref. 213), 229, *261*
Greene, F. D., 387 (ref. 114), *419*
Gregory, J. T., 237 (ref. 93), 238 (ref. 92), 239 (refs. 91, 92), *258*
Greidanus, J. W., 121 (ref. 20), 140 (ref. 20), 141 (ref. 20), 146–148 (ref. 20), 155 (ref. 20), 156 (ref. 20), 159 (ref. 20), 161 (ref. 20), 163 (ref. 20), 184 (ref. 20), 186–188 (ref. 20), *207*
Gresham, T. L., 197 (ref. 191), *212*, 236 (ref. 83), 237, 238 (refs. 89; 90, 92, 97, 98), 239 (refs. 85–87, 91, 92, 94, 99, 100), *257*, *258*
Gresham, W. F., 223 (ref. 101), *258*
Greuter, F., 377 (ref. 115), *419*
Grigsby, W. E., 224 (ref. 102), *258*
Grimison, A., 318 (ref. 101), *327*
Groenhuyzen, G., 127 (ref. 187), 128 (ref. 187), 151 (ref. 187), 154 (ref. 187), 196 (ref. 187), *212*
Gros, A., 407 (ref. 124), 408 (ref. 124), 410 (ref. 124), *420*
Gross, E. v., 383 (ref. 122), 384 (ref. 122), *420*
Grossman, H., 381 (ref. 216), *422*
Groszos, S. J., 196 (ref. 146), *211*
Grove, J. F., 319 (ref. 104), *328*
Gruber, W., 100 (refs. 61, 62), *113*
Grünager, D., 195 (ref. 188), *212*
Grütter, H., 159 (ref. 97), 161 (ref. 97), *209*
Grummitt, O., 400 (ref. 117), *419*
Gryszkiewicz-Trochimowski, E., 142 (ref. 59), *208*
Gryskiewicz-Trochimowski, O., 142 (ref. 59), *208*
Günther, F., 334 (ref. 22), 360 (ref. 22), *363*
Guia, M., 390 (ref. 118), *419*
Guillemonat, A., 4 (ref. 25a), *63*
Gunar, B. I., 246 (refs. 186, 189), 247 (ref. 189), *260*
Gusev, B. P., 246 (refs. 186, 188, 189), 247 (refs. 188, 189), 248 (ref. 188), *260*
Gutowsky, H. S., 241 (ref. 10), *256*, 266, 274, 275 (ref. 3), 277 (ref. 15), 278, 280 (ref. 3), 284 (ref. 3), 292 (ref. 33), 293, 295 (refs. 35, 40), 296 (refs. 33, 51), 302 (refs. 35, 40), 304 (ref. 40), 307, 309 (refs. 40, 56, 60), 310 (refs. 33, 61, 62), 312, 313, *325–327*

Gutsche, C. D., 410 (ref. 119), *419*
Gwynn, B. H., 224, *257*
Gyermek, L., 82 (ref. 63), *113*

H

Häfliger, F., 434 (ref. 18), 446 (refs. 15–18), 450 (ref. 46), 453 (ref. 18), *454*, *455*
Hagemeyer, H. J., 215, 219 (ref. 104), 222 (ref. 103), 223 (ref. 103), 224, 225 (ref. 103), 226, 227 (refs. 103, 112, 113), 228, 229 (ref. 103), 233–235 (ref. 118), 237 (ref. 103), 240 (refs. 115, 116), 252, 254, *258*
Hager, G. F., 353 (refs. 89, 92), *365*
Hahn, E. L., 292 (ref. 34), 296 (refs. 34, 50), 301 (ref. 34), 302, *325*, *326*
Hamalainen, C., 217 (ref. 119), *258*
Hammond, G. S., 373 (ref. 311), *425*
Hancock, J. E. H., 316 (ref. 91), *327*
Hanewald, K. H., 404 (ref. 200), *422*
Hanford, W. E., 214 (ref. 120), 215, *258*
Hannah, J., 340 (ref. 39), 348, *364*
Hansen, W. W., 265, 272, *326*
Hanson, J. E., 118, 121 (ref. 3), 122 (ref. 3), 126, 127 (ref. 3), 156 (ref. 3), 163 (ref. 3), 164 (ref. 3), 167 (ref. 3), 168 (ref. 3), 184 (ref. 3), 189 (ref. 3), *206*
Harborth, G., 2 (ref. 87b), *65*
Hardegger, E., 87 (ref. 63a), *114*, 434 (ref. 5), 440, 441 (refs. 22, 23, 42), 442 (refs. 3, 4, 42), 443 (refs. 3, 4), 444 (refs. 3–5), 446 (ref. 5), 453 (ref. 5), *453–455*
Harhash, A. H. E., 375 (ref. 178), 386 (ref. 178), *421*
Harley-Mason, J., 239 (refs. 121, 122), 249 (ref. 121), *258*
Harnack, E., 428, *454*
Hart, H., 336 (ref. 26), *363*
Hartley, G. S., 402, *419*
Hartung, W. H., 81 (ref. 73a), *114*
Hasek, W. R., 387 (ref. 318), *425*
Haskelberg, L., 345 (ref. 61), *364*
Hasselstrom, T., 374 (ref. 34), 378 (ref. 34), *417*
Hata, Y., 71, *114*
Hatch, L. F., 121 (ref. 31), 124, 127 (ref. 31), 129 (ref. 31), 151 (ref. 31), 153 (ref. 31), 155 (ref. 31), *207*
Hatchard, W. R., 141 (ref. 47), *208*
Haubein, A. H., 2 (ref. 24), *63*
Haury, V. E., 231 (ref. 123), *259*
Hauser, C. H., 235 (ref. 175), *260*
Havinga, E., 403 (refs. 279, 280), 404 (refs. 201, 330), 405 (ref. 121), *419*, *422*, *424*, *425*
Hayao, S., 238
Haynes, G. R., 399 (ref. 112), *419*
Hazenberg, J. F. A., 149 (ref. 82), *209*
Heberling, J., 144 (ref. 77), *209*
Heckert, R. E., 334 (ref. 21), *363*
Heilbron, I., 120, 122 (ref. 15), 130 (ref. 15), 132–134 (ref. 15), 159 (ref. 15), 161 (ref. 15), *207*
Heine, R. F., 144 (ref. 73), 185 (ref. 73), *209*
Heinrich, P., 411 (ref. 62), *418*
Heiss, H., 409 (ref. 261), *423*
Hekkert, G. L., 127 (ref. 193), 128 (ref. 193), 146 (ref. 193), 169 (ref. 193), 196 (ref. 185), *212*
Heldman, J. D., 372 (ref. 32), *417*
Helferich, B., 383 (ref. 122), 384 (ref. 122), *420*
Henbest, H. B., 334 (ref. 20), *363*
Hende, J. H., van den, 121 (ref. 20), 140 (ref. 20), 141 (ref. 20), 146–148 (ref. 20), 155 (ref. 20), 156 (ref. 20), 159 (ref. 20), 161 (ref. 20), 163 (ref. 20), 184 (ref. 20), 186–188 (ref. 20), *207*
Henderson, A. W., 402 (ref. 59), *418*
Henery-Logan, K. R., 174 (ref. 130), *210*
Hermans, A. C., 186 (ref. 142), 187 (ref. 142), *211*
Hertler, W. R., 377 (ref. 85), *418*
Heslinga, L., 165 (refs. 119, 120), 166 (ref. 120), 173 (ref. 119), *210*
Hess, H-J., 404 (ref. 133), *420*
Hess, K., 347 (refs. 70, 71), *364*
Heuschkel, V., 375 (ref. 323), 415 (ref. 323), *425*

Heusler, K., 135 (ref. 101), 137 (ref. 101), 159–163 (ref. 101), *209*
Heusner, A., 75 (ref. 123), 77, 82 (ref. 64), 86 (ref. 121), 87, 88 (ref. 121), 89 (refs. 65, 122), *114*, *115*
Heusser, H., 134 (ref. 89), 159 (ref. 89), 161 (refs. 89, 106), 162 (ref. 106), *209*, *210*
Higashigaito, T., 241 (ref. 142), *259*
Hildahl, G. T., 341 (ref. 48), *364*
Hilditch, T. P., 350 (ref. 79), *365*
Hill, H. E., 119 (ref. 5), 140–143 (ref. 5), 145–147 (ref. 5), 151 (ref. 5), 153 (ref. 5), 185 (ref. 5), *207*
Hirsch, D. H., 234 (ref. 124), *259*
Hirshberg, Y., 373 (refs. 26, 282), *417*, *424*
Hlavka, J. J., 174, *211*
Hoaglin, R. I., 234 (ref. 124), *259*
Hoán, Ng., 339, *364*
Hodosan, F., 389 (ref. 266), *424*
Hoehn, H. H., 192, *210*
Hoffman, C. H., 317 (ref. 96), *327*, 361, *366*
Hogevan, H., 164 (ref. 199), *212*
Hohn, R. T., 233 (ref. 177), *260*
Holley, R. W., 221 (ref. 24), *256*
Holm, C. H., 293 (ref. 40), 295 (ref. 40), 302 (ref. 40), 304 (ref. 40), 309 (ref. 40), 312, 313, *326*, *327*
Honda, J., 428, *454*
Hopff, H., 227 (ref. 125), *259*
Horner, L., 334, 363, 383 (ref. 123), 407 (refs. 124, 125), 408 (refs. 124, 147, 321), 409 (ref. 127), 410 (ref. 124), 412 (ref. 128), 415 (ref. 126), *420*, *425*
Horton, A. T., 375 (ref. 36), *417*
House, H. O., 389 (ref. 316), *425*
Hoyle, K., 353 (ref. 89), *365*
Hudec, J., 389 (ref. 84), 390 (ref. 84), 391 (ref. 82), *418*
Hudson, F. L., 400 (ref. 185), *421*
Hüssy, H., 347 (ref. 66), *364*
Hufford, D. L., 80, *114*
Huggins, M. L., 279, 280 (ref. 11), *325*
Huisgen, R., 414 (ref. 129), *420*
Hull, D. C., 215, 233–235 (ref. 118), *258*
Hurd, C. D., 216 (refs. 133, 138), 217, 218 (refs. 127, 132), 224 (ref. 134), 225 (ref. 134), 228, 230, 238, 240, 241, 252, 253 (ref. 137), 255 (ref. 137), *259*
Hurst, J. J., 392 (ref. 308), *425*
Hutton, T. W., 406 (ref. 91), 407 (ref. 286), 408 (ref. 286), *419*, *424*
Huyser, E. S., 415 (ref. 271), *424*

I

Ikeda, Y., 241 (ref. 142), *259*
Imperial Chemical Industries, Ltd., 68 (ref. 68), 69 (ref. 68), 73 (ref. 70), 74 (ref. 70), 80 (refs. 69, 71), *114*
Inhoffen, H. H., 131 (ref. 110), 161 (ref. 110), 200, *210*, *211*, 400 (refs. 130, 131), 404 (refs. 132, 133, 331), *420*, *425*
Inman, C. G., 379 (ref. 47), *417*
Inscoe, M. N., 402 (ref. 314), *425*
Ionescu, M., 413 (ref. 265), *423*
Iotsitch, 24 (ref. 26), *63*
Irmscher, K., 404 (refs. 132, 331), *420*, *425*
Isaev, Yu. B., 217 (refs. 203, 204), 218 (ref. 205), *261*
Isidate, M., 382 (ref. 134), *420*
Islam, A. M., 384 (ref. 173), *421*
Isler, O., 121 (ref. 34), 125 (ref. 34), 131–133 (ref. 34), 154 (ref. 34), 158 (ref. 34), 161–163 (ref. 34), *207*, 248 (ref. 143), *259*
Ismail, A. F., 414 (ref. 226), *422*
Isoshima, T., 217 (ref. 145), 225, *259*
Iwakwa, Y., 238 (ref. 146), *259*

J

Jackman, L. M., 267, 319 (ref. 105), 323 (ref. 114), *328*, 329–366
Jackson, C. L., 335, 359 (refs. 112, 113), *363*, *366*
Jacobs, T. L., 118, 121 (refs. 3, 21, 32), 122 (ref. 3), 123 (refs. 21, 35), 124, 126, 127 (refs. 3, 21, 39, 40), 129 (refs. 21, 32, 41), 130 (ref. 21), 140, 153 (ref. 21), 154 (ref. 21), 156 (refs. 3, 41), 157 (ref. 21), 163 (ref. 3), 164, 167

(ref. 3), 168 (ref. 3), 184 (ref. 3), 189 (refs. 3, 32), 190, 193, 194 (refs. 32, 40), 198 (ref. 21), *206–208*, *210*, *211*, 319 (ref. 103), *328*
Jäger, A., 232, *261*
Jaffe, H. H., 13 (ref. 71a), *64*
Jansen, J. E., 197 (ref. 191), *212*, 236 (ref. 83), 237 (refs. 84, 88, 93), 238 (refs. 89, 90, 92), 239 (refs. 85–87, 91, 92, 94), *257*, *258*
Jarrett, H. S., 280 (ref. 81), *327*
Jeger, O., 377 (refs. 53, 115, 325), 395 (ref. 3), 396 (ref. 100), 397 (ref. 272), 405 (ref. 135), *416*, *418–420*, *424*, *425*
Jellinek, F., 428 (ref. 30), 431 (ref. 31), 432–434 (ref. 30), 436 (ref. 30), 437, 439, 449 (ref. 30), *454*
Job, 7, *63*
John, Fr., 331, 334 (ref. 5), *363*
John, G. S., 329
Johns, C. H., 329
Johns, W. F., 135 (refs. 100a, 100b), 159 (refs. 100a, 100b), 160 (refs. 100a, 100b), *209*
Johnson, A. W., 68 (ref. 67), *114*, 200 (ref. 151), *211*
Johnson, F., 222 (ref. 147), *259*
Johnson, F. E., 220 (ref. 50), *257*
Johnson, H. E., 410 (ref. 119), *419*
Johnson, J. R., 240 (ref. 148), *259*
Jolley, J. E., 372 (ref. 183), *421*
Jones, D. G., 68, 69 (ref. 68), 73, 74 (ref. 70), 80, *114*
Jones, E. R. H., 25, 26, *63*, 120, 122, 127 (refs. 17, 33), 128 (ref. 17), 130 (ref. 15), 132–134 (ref. 15), 154 (refs. 17, 33), 159 (ref. 15), 161 (ref. 15), 164 (ref. 17), 169 (ref. 17), 171 (ref. 17), *207*, 404 (ref. 60), *418*
Jones, W. M., 219 (ref. 20), *256*
Jong, A. W. K. de, 387 (ref. 136), *420*
Jonge, J. de, 402 (ref. 139), 408 (ref. 137), 415 (ref. 138), *420*
Jorgensen, M. J., 389 (ref. 294), 390 (ref. 294), 416 (ref. 294), *424*
Jorgensen, P. F., 402 (ref. 296), *424*
Jucker, E., 78, 79, 82 (ref. 106), 83, 86 (ref. 105), 107, *114*, *115*
Jürgens, E., 412 (ref. 128), *420*
Julia, M., 26, 27, 56 (ref. 31), *63*, 120, 122 (ref. 15), 130 (ref. 15), 132–134 (ref. 15), 159 (refs. 14, 15), 161 (ref. 15), 201, *207*, *211*
Juster, N., 193 (ref. 150), 194 (ref. 150), *211*
Jutz, C., 30 (ref. 31b), *63*
Juveland, O. O., 415 (refs. 270, 271), *424*

K

Kaarsemaker, S., 230 (ref. 149), *259*
Kaesz, H. D., 13 (ref. 1a), *62*
Kahle, G. R., 130 (ref. 169), 151 (ref. 169), 153, 161 (ref. 169), *211*
Kaiser, S., 246–248 (ref. 154), *259*
Kalman, A., 218 (ref. 171), *260*
Kalvoda, J., 377 (refs. 53, 115), *418*, *419*
Kamel, M., 385 (ref. 177), *421*
Kamlet, M., 412 (ref. 140), *420*
Kaplan, L., 412 (ref. 140), *420*
Kappeler, H., 130 (ref. 98), 159 (refs. 97, 98), 161 (ref. 97), *209*
Karbinos, J. V., 350 (ref. 83), *365*
Karlsoi, P., 382 (ref. 56), *418*
Karplus, M., 310, *326*, *328*
Karrer, P., 75 (ref. 74), 77, 79, 84, 86 (ref. 74), 87 (ref. 74), 89, *114*, 437 (ref. 21), *454*
Katerberg, G. J., 165 (ref. 120), 166 (ref. 120), *210*
Katz, L., 241 (ref. 150), *259*
Kauffmann, J., 380 (ref. 51a), *417*
Kaufmann, A., 347 (ref. 66), *364*
Kaufmann, P., 93, *115*
Kawasumi, H., 238 (ref. 146), *259*
Kaye, I. A., 318 (ref. 100), *327*
Keagle, L. C., 81 (ref. 73a), *114*
Kearby, K. K., 329
Kebrle, J., 75 (ref. 74), 77, 79, 84, 86 (ref. 74), 87 (ref. 74), 89, *114*
Keefer, R. M., 331 (ref. 13), *363*
Kelso, C. D., 253 (ref. 137), 255 (ref. 137), *259*

Kempf, R., 412 (ref. 209), *422*
Kende, A. S., 406 (ref. 16), *416*
Kenyon, J., 374 (ref. 141), *420*
Kharasch, M. S., 4 (ref. 32), 7, *63*, 369 (ref. 142), 378, 381 (ref. 146), 414 (ref. 144), 415 (ref. 145), *420*
Kharasch, N., 141 (refs. 51, 52), 142 (ref. 52), *208*
Khôi, Ng. H., 339, 342 (ref. 51), *364*
Kieslich, K., 131 (ref. 167), *211*
Kigawa, S., 238 (ref. 146), *259*
Kimball, G. E., 299 (ref. 70), *326*
Kimel, W., 242 (ref. 152), 245, 246, 247 (refs. 153–155), 248 (refs. 153–155), *259*
King, H., 428, 429 (ref. 27), 436, *454*
Kinkel, K. G., 403 (ref. 326), *425*
Kirchhof, W., 339 (ref. 38), *364*
Kirmse, W., 407 (ref. 322), 408 (ref. 147), *420*, *425*
Kirrmann, A., 2 (ref. 34), 3 (ref. 35), 24, *63*
Kiss, J., 441 (ref. 42), 442 (ref. 42), *455*
Kistiakowsky, G. B., 372 (ref. 148), 381 (ref. 24), *417*, *420*
Kläning, V. K., 414 (ref. 309), *425*
Kleiderer, E. C., 350 (ref. 80), 354 (refs. 80, 94), *365*
Klein, J., 406 (ref. 22), *417*
Klever, H. W., 214 (ref. 232), *262*
Klinger, H., 383 (ref. 149), 387 (ref. 149), *420*
Klingsberg, A., 358 (ref. 111), *366*
Knight, W. D., 273, *325*
Knox, L. H., 410 (ref. 97), *419*
Kny, H., 314 (ref. 86), *327*
Koch, K., 399 (ref. 307), *425*
Kocheschov, K. A., 219 (ref. 221), *261*
Kock, R. J. de, 403 (ref. 329), 404 (refs. 329, 330), *425*
Kock, S. D., 241 (ref. 178), *260*
Koczor, I., 84, *113*
Kögl, F., 428, 429 (ref. 28), 431 (ref. 31), 432, 433 (ref. 30), 434 (refs. 5, 30), 435, 436 (ref. 30), 439, 440, 442 (refs. 3, 4), 443 (refs. 3, 4), 444, 446 (ref. 5), 449, 453, *453*, *454*
Koerts, D. H., 177 (ref. 133), 182 (ref. 138), *210*, *211*
Köser, J., 406 (ref. 289), *424*
Köster, R., 230 (ref. 173), *260*
Koevoet, A. L., 403 (ref. 279), 405 (ref. 121), *419*, *424*
Kofron, J. T., 380 (ref. 49), *417*
Koizumi, M., 414 (ref. 150), *420*
Koller, E., 380 (ref. 49), *417*
Koltzenburg, G., 381 (ref. 216), *422*
Kolvenbach, W., 383 (ref. 149), 387 (ref. 149), *420*
Komarewsky, V. I., 329
Konzett, H., 83 (ref. 97), *115*
Koppe, R., 428, 429 (ref. 38), *454*
Kornfeld, E. C., 93, *114*, 350 (ref. 80), 354 (ref. 80), *365*
Kosak, A. I., 342 (ref. 52), *364*
Koszalka, T. R., 80, *114*
Krane, W., 408 (ref. 328), *425*
Krasnaya, Zh. A., 121 (ref. 171), 123 (ref. 171), 124 (ref. 171), 127 (ref. 171), 130 (ref. 171), 131 (ref. 171), 159 (ref. 171), 161 (ref. 171), *212*
Krebaum, L. J., 395 (ref. 3), *416*
Krebs, H., 77, *114*
Krespan, C. G., 334 (ref. 21), *363*
Krestinsky, W., 3 (ref. 37), *63*
Kritzler, H., 130 (ref. 161), 158, 159 (ref. 161), *211*
Kröhnke, F., 412 (ref. 152), 414 (ref. 151), *420*
Kröhnke, G., 414 (ref. 151), *420*
Kruptsov, B. K., 246 (ref. 187), 247 (ref. 187), *260*
Krynitsky, J. A., 216 (refs. 251, 252), 229 (ref. 253), *262*
Kubler, D. G., 234 (ref. 124), *259*
Kuchler, L., 413 (ref. 153), *420*
Kuderna, B. M., 378 (ref. 143), *420*
Kuderna, J., 378 (ref. 146), 381 (ref. 146), *420*
Kuehl, F. A., 432, 433 (ref. 34), 434 (ref. 34), 436, *454*
Kühnel, M., 221 (ref. 235), *262*
Küng, F. E., 226 (ref. 157), *259*
Kuhn, R., 218 (ref. 156), *259*

Kulka, M., 347 (ref. 65), *364*
Kullnig, R. K., 280, 309 (ref. 19), 322 (ref. 112), *325*, *328*
Kumler, W. D., 314 (ref. 84), *327*
Kundiger, D., 168 (ref. 128a), 180 (ref. 128a), *210*
Kuroda, A., 414 (ref. 150), *420*
Kwiatik, J., 231, *256*

L

Laan, P. J. van der, 428 (ref. 29), *454*
Laber, G., 318 (ref. 99), *327*
Lacey, R. N., 213–263
Ladewig, H., 400 (ref. 253), *423*
Laidler, K. J., 400 (ref. 113), *419*
Lalande, R., 387 (ref. 320), *425*
Landmann, H., 144 (ref. 72), 150 (ref. 72), *209*
Landquist, J. K., 411 (ref. 154), *420*
Langella, M. R., 195 (ref. 188), *212*
Langham, W., 2 (ref. 23), *63*
Lardon, A., 136 (ref. 112), 159 (ref. 112), 161–163 (ref. 112), *210*
Lasco, R., 82 (ref. 80), *114*
Latif, N., 374 (ref. 232), 383 (refs. 229, 231–233), 384 (ref. 232), 385 (ref. 230), 386 (ref. 232), *423*
Laubach, G. D., 344, *364*
Laws, G. F., 406 (ref. 91), *419*
Lawson, W. B., 316 (ref. 94), *327*
Lebel, N., 432, 433 (ref. 34), 434 (ref. 34), 436 (ref. 34), *454*
Lecher, H. Z., 249 (ref. 170), *260*
Leder-Packendorff, L., 233 (ref. 193), *260*
Leditschke, H., 100 (refs. 77–79), *114*
Leebrick, J. R., 4 (ref. 70b), *64*
Lehfeldt, A., 389 (ref. 247), *423*
Lehmann, G., 81, *115*
Leighton, P. A., 413 (ref. 155), 414, *420*
Lemieux, R. U., 280, 309 (ref. 19), 322 (ref. 112), *325*, *328*
Lerner, O. M., 249 (ref. 195), *261*
Leton, J. R., 321 (ref. 109), *328*
Letsinger, R. L., 2 (ref. 45), *64*, 82 (ref. 80), *114*, 373 (ref. 199), *422*
Lettré, H. H., 403 (ref. 156), *420*
Leusen, A. M. van, 198 (ref. 186), *212*
Levin, S. H., 323 (ref. 115), *328*, 394 (ref. 273), *424*
Levisalles, J., 69 (ref. 81), 74 (ref. 81), 80, 82 (refs. 81, 82), *114*, 394 (ref. 19), *416*
Lévy, G., 230 (ref. 56), *257*
Levy, R. H., 356 (ref. 105), 357 (ref. 105), *365*
Levy, V., 8 (ref. 39), 51 (ref. 39), 52 (refs. 38, 39), 53 (ref. 39), 56 (ref. 39), 59 (ref. 39), *63*
Lewis, G. N., 400 (ref. 157), *421*
Lewis, R. N., 7, *63*
Li, C., 218 (ref. 171), *260*
Li, S.-O., 74 (ref. 23), 104 (ref. 23), 105 (ref. 23), 110 (ref. 23), *112*
Lichtarowicz, A., 340 (ref. 42), *364*
Liddel, U., 280 (refs. 22, 31), 286 (ref. 31), *325*
Liechti, P., 434 (ref. 5), 441 (ref. 23), 444 (ref. 5), 446 (ref. 5), 453 (ref. 5), *453*, *454*
Limaye, D. B., 374 (ref. 158), *421*
Limborg, F., 68 (ref. 26), 69 (refs. 19, 26), 70 (refs. 24, 27, 83), 71 (refs. 20, 22, 27), 72 (refs. 20, 21), 74 (ref. 20), 82 (ref. 19), 86 (ref. 25), 107 (ref. 27), 110 (ref. 21), *112*
Lindenfors, S., 400 (ref. 319), *425*
Lindenmann, A., 78, 83 (refs. 108–110, 112), 107, *115*
Lindlar, H., 162 (ref. 109), 189 (ref. 109), 201 (ref. 196), *210*, *212*
Linn, B. O., 317 (ref. 96), *327*
Linstead, R. P., 330 (ref. 1), 331 (refs. 7–10), 332 (ref. 7), 333 (refs. 7, 16), 335 (ref. 10), 336 (ref. 27), 337 (ref. 10), 338 (refs. 10, 16), 340 (refs. 39, 42–44), 342 (ref. 53), 348, 350 (refs. 84–87), 351, 354, *363–365*, 440, *454*
Lipinsky, E. S., 379 (ref. 47), *417*
Lipkin, D., 400 (ref. 157), *421*
Lipmann, F., 233 (ref. 229), *262*
Lipp, P., 230 (refs. 172, 173), *260*
Lipscomb, W. N., 241 (ref. 150), *259*
Lister, J. H., 437 (ref. 21), *454*

Litle, R. L., 387 (ref. 2), 409 (ref. 60a), *416*, *418*
Little, E. L., 2 (ref. 45), *64*, 334 (ref. 21), *363*
Loewus, F. A., 356 (refs. 105, 108), 357 (ref. 105), *365*, *366*
Logothetis, A., 342 (ref. 50), *364*
Lohse, F., 434 (ref. 5), 441 (refs. 22, 23), 444 (ref. 5), 446 (ref. 5), 453 (ref. 5), *453*, *454*
Looney, C. E., 313 (ref. 77), *327*
Lornitzo, F., 84, *115*
Lowe, G., 331 (ref. 10), 335 (ref. 10), 337 (ref. 10), 338 (refs. 10, 34), *363*
Lown, J. W., 337 (ref. 30), *363*
Lucy, F. A., 413 (ref. 155), 414, *420*
Lukes, R., 35 (refs. 12, 12a), *62*, *63*
Lukes, R. M., 135 (refs. 100a, 100b), 159 (refs. 100a, 100b), 160 (refs. 100a, 100b), *209*
Lukyanova, L. D., 247 (ref. 208), *261*
Lund, K., 402 (ref. 159), *421*
Lunstead, L. G., 353 (ref. 93), *365*
Lupas, I., 412 (ref. 238), *423*
Lutsenko, I. F., 236 (ref. 190), *260*
Lutz, R. E., 104, *113*, 400 (ref. 160), *421*
Lyashenko, V. D., 240 (ref. 174), *260*
Lyons, A. L., 2 (ref. 45), *64*

M

Macbeth, A. K., 330 (ref. 4), *363*
McCall, D. W., 277 (ref. 15), 278, 292 (ref. 33), 296 (refs. 33, 51), 310 (ref. 33), 312, *325*, *326*
McCollum, J. D., 348 (ref. 77), *365*
McCombie, H., 144 (ref. 76), *209*
McConnell, H. M., 281, 285 (ref. 28), 295 (ref. 38), 296 (ref. 38), 300, 307, 308 (ref. 72), 311, *325–327*
McDonnell, C. H., 415 (ref. 270), *424*
McElvain, S. M., 168 (refs. 128, 128a), 180, *210*
McGarvey, B. R., 277 (ref. 15), 278, *325*
McGee, J., 236 (ref. 3), *255*
McGehee, J. W., 220 (ref. 214), 221 (ref. 214), *261*
McHugh, G. P., 402 (ref. 39), *417*
McKenna, J. F., 168 (ref. 126), *210*
McLaughlin, P. J., 347 (ref. 69), *364*
MacLaurin, R. D., 335 (ref. 24), 359 (ref. 112), *363*, *366*
McLean, A. D., 295 (ref. 38), 296 (ref. 38), 300 (ref. 38), 305 (ref. 38), 307 (ref. 38), *326*
MacLean, A. F., 214 (ref. 77), *257*
McLean, M. J., 403 (ref. 27), *417*
McLeish, E. L., 400 (ref. 195), *422*
McManimie, R. J., 144 (refs. 73–75), 185 (ref. 73), *209*
MacMillan, J., 319 (ref. 104), *328*
MacMillan, W. G., 127 (ref. 39), 140, *208*
McMurry, T. B., 395 (ref. 80), *418*
McNesby, J. R., 372 (ref. 167), *421*
McPherson, J. P., 317 (ref. 96), *327*
Maekawa, H., 446 (ref. 43), *455*
Magatti, E., 361 (ref. 116), *366*
Magel, T. T., 241 (ref. 130), *259*, 400 (ref. 157), *421*
Maggiolo, A., 354 (ref. 100), *365*
Magrath, D., 159 (ref. 91), *209*
Mahncke, H. E., 400 (ref. 161), *421*
Maier, L., 12, 42 (ref. 41), *63*
Maioli, L., 142, *212*
Maitte, P., 4 (ref. 42a), 8 (ref. 57), 26 (ref. 59), 28, 35 (refs. 57, 60), 51 (refs. 42, 60), 52 (ref. 59), 53 (ref. 59), 56 (refs. 42, 59), 59 (ref. 42, 59), 60 (ref. 59), 62 (refs. 42, 57), *63*, *64*
Makhailov, B. M., 411 (ref. 162), *421*
Makin, S. M., 246 (refs. 187, 188), 247 (refs. 187, 188), 248 (ref. 188), *260*
Mann, E. H., 235 (ref. 175), *260*
Mannich, C., 157 (ref. 113), *210*
Manning, P. P., 372 (ref. 163), *421*
Manske, R. H. F., 347 (ref. 65), *364*
Manson, A. J., 350 (ref. 82), *365*
Mansour, A. K. E., 375 (ref. 178), 386 (ref. 178), *421*
Manuel, T. A., 315 (ref. 89), *327*
Marbet, R., 201 (ref. 196), *212*
Marei, A. A., 69 (ref. 83a), 71 (ref. 83a), 72 (ref. 83a), 75 (ref. 83a), 81, *114*
Margerum, J. D., 380 (ref. 315), *425*

Marhenkel, E., 118 (ref. 3a), 141 (ref. 3a), *206*
Maroney, W., 400 (ref. 187), *421*
Marsh, F. D., 2 (ref. 45), *64*
Martin, G., 2 (ref. 44), 5 (ref. 63), 14 (ref. 63), 15 (ref. 63), 29, 33 (ref. 44), 40 (ref. 43), 44 (ref. 63), 45 (ref. 63), 61 (refs. 43, 44), *63*, *64*
Martin, R. B., 373 (ref. 199), *422*
Marx, A. F., 120 (ref. 163), 172 (ref. 163), 174 (ref. 163), *211*
Mar'yanovskaya, K. Y., 219 (ref. 206), *261*
Masson, C. R., 368 (ref. 165), 372 (ref. 164), *421*
Matsumoto, T., 446 (ref. 43), *455*
Mawer, F., 224 (ref. 176), *260*
Maxwell, D. E., 292 (ref. 34), 296 (refs. 34, 50), 301 (ref. 34), 302, *325*, *326*
Mayer, J. R., 410 (ref. 98), *419*
Maynert, E. W., 141 (ref. 47), *208*
Mayo, G. L., 143 (ref. 200), 146 (ref. 200), *212*
Mayo, P. de, 367–425
Meakins, G. D., 404 (ref. 60), *418*
Meerwein, H., 410 (ref. 168), *421*
Meinel, K., 69, *114*
Meinwald, J., 82 (ref. 85), *114*
Meinwald, Y. C., 315 (ref. 90), *327*
Meister, P. D., 356 (ref. 104a), *365*
Melstrom, D. S., 233 (ref. 177), *260*
Merck, F., 347 (ref. 71), *364*
Merkel, F., 402 (ref. 287), *424*
Mertens, H.-J., 403 (ref. 326), *425*
Merz, H., 334, *363*, 388 (ref. 123), *420*
Metzger, H., 375 (ref. 323), 415 (ref. 323), *425*
Meyer, H., 414 (ref. 169), *421*
Meyer, L. H., 265, 266 (ref. 3), 274 (ref. 3), 275 (ref. 3), 277 (ref. 15), 278, 280 (ref. 3), 284 (ref. 3), *325*
Michaelis, A., 348 (ref. 75), *365*
Michl, K. H., 249 (ref. 246), *262*
Middleton, W. J., 334 (ref. 21), *363*
Miescher, K., 374 (ref. 30), 382 (ref. 30), *417*
Miginiac, L., 9 (ref. 44a), 17 (ref. 44a), *64*
Milas, N. A., 139 (ref. 170), 151 (ref. 170), *212*
Miller, A., 372 (ref. 33), *417*
Miller, E. H., 4 (ref. 70b), *64*
Miller, F. A., 241 (ref. 178), *260*
Miller, U., 401 (ref. 189), *421*
Mills, J. S., 382 (ref. 303), *425*
Minnaard, N. G., 404 (ref. 330), *425*
Mironov, V. F., 10 (ref. 69a), *64*
Miropol'skaya, M. A., 159 (ref. 154), 200, *211*, 247 (refs. 207, 208), 248 (ref. 207), *261*
Misrock, S. L., 387 (ref. 114), *419*
Mitchell, P. W. D., 350 (refs. 84, 87), 351 (refs. 84, 87), *365*
Mochalin, V. B., 246 (ref. 187), 247 (ref. 187), *260*
Mochel, W. E., 414 (ref. 170), *421*
Modderman, P., 120 (ref. 16), 130 (ref. 105), 161 (ref. 105), 169 (ref. 16), 171 (ref. 16), *207*, *210*
Modena, G., 142, 149 (ref. 81), *209*, *212*
Möller, K., 409 (refs. 260–262), *423*
Moffer, R. F., 143 (ref. 200), 146 (ref. 200), *212*
Moffett, R. B., 234, *260*
Moir, R. Y., 322 (ref. 112), *328*
Montanari, F., 119 (ref. 3b), 140, 141 (refs. 42, 43, 45, 46, 55, 66), 142, 144 (refs. 78, 79), 145, 146 (refs. 3b, 42, 43), 147 (ref. 68), 149 (refs. 80, 81), 153 (ref. 43), 154 (refs. 42, 43), 184 (refs. 3b, 42, 43), 185 (ref. 43), *206*, *208*, *209*
Montavon, M., 121 (ref. 34), 125 (ref. 34), 131–133 (ref. 34), 154 (ref. 34), 158 (ref. 34), 161–163 (ref. 34), *207*
Moore, A. M., 415 (ref. 171), *421*
Moore, F. W., 2 (ref. 23), *63*
Moore, P. T., 316 (ref. 93), *327*
Moore, R. F., 383 (ref. 172), 386 (ref. 172), *421*
Moore, W. M., 373 (ref. 311), *425*
Moore, W. R., 316 (ref. 93), *327*
Morey, G. H., 216, 217 (ref. 180), *260*

Morf, R., 142 (ref. 58), *208*
Morisson, G. C., 3 (ref. 2a), *62*
Morita, H., 141 (ref. 65), *208*
Morris, D. S., 159 (ref. 91), *209*
Morris, R., 319 (ref. 106), 320 (ref. 106), *328*
Morton, A. A., 2, *64*
Mosher, H. S., 93, *115*
Moubasher, R., 374 (refs. 222, 232), 383 (refs. 219, 229, 232), 384 (ref. 232), 385 (ref. 230), 386 (refs. 219, 232), *422*, *423*
Mousa, G. A., 376 (ref. 234), 386 (ref. 234), *423*
Mucahy, E. N., 383 (ref. 122), 384 (ref. 122), *420*
Muders, R., 408 (ref. 328), *425*
Müller, E., 375 (ref. 323), 415 (ref. 323), *425*
Müller, G., 432 (ref. 12), 434 (refs. 12, 41), 435 (ref. 41), *454*, *455*
Müller, K., 231, *262*
Müller, W., 414 (ref. 78), *418*
Mugdan, M., 229 (ref. 181), *260*
Muhlmann, R., 414 (ref. 42), *417*
Mulholland, T. P. C., 319 (ref. 104), *328*
Murad, E., 372 (ref. 313), *425*
Murakami, M., 71, *114*
Murray, H. C., 356 (ref. 104a), *365*
Murray, M. J., 241 (ref. 240), *262*
Musher, J., 314 (ref. 83), *327*
Mustafa, A., 336 (ref. 28), *363*, 373 (refs. 221, 227), 374 (refs. 174, 220), 375 (refs. 178, 221), 383 (refs. 174, 175, 227–229), 384 (refs. 173, 223, 225), 385 (ref. 177), 386 (ref. 178), 387 (ref. 176), *421–423*
Muth, K., 408 (ref. 321), *425*
Muths, R., 24 (ref. 36), *63*
Mylo, B., 80, *115*

N

Naar-Colin, C., 280 (refs. 13, 14), 281, 284, 285, 286 (refs. 13, 14), 287, 291 (ref. 64), 307, *325*, *326*
Nádor, K., 82 (ref. 63), *113*
Nagakubo, K., 238 (ref. 146), *259*
Nair, P. M., 313 (ref. 79), 314 (ref. 79), *327*
Nakasaki, M., 347 (ref. 74), *365*
Napier, D. R., 409 (ref. 60a), *418*
Naves, Y. R., 121 (ref. 27), 123 (ref. 27), 127 (ref. 27), 131 (ref. 27), 159 (ref. 27), 161 (ref. 27), 163 (ref. 27), *207*, 246, 247, 248 (refs. 183–185), *260*
Nazarov, D. V., 246 (ref. 187), 247 (ref. 187), *260*
Nazarov, I. N., 27 (ref. 46), 52 (ref. 46), 58 (ref. 46), *64*, 121 (ref. 171), 123 (ref. 171), 124 (ref. 171), 127 (ref. 171), 130 (ref. 171), 131 (ref. 171), 159 (ref. 171), 161 (ref. 171), *212*, 246, 247 (refs. 187–189), 248 (ref. 188), *260*
Nazarova, I. I., 246 (refs. 187, 188), 247 (refs. 187, 188), 248 (ref. 188), *260*
Nedenskov, P., 71 (ref. 87), 74 (ref. 87), 82 (refs. 50, 50a), 84, 86 (ref. 25), 93, 94 (ref. 28), 97 (ref. 29), 101 (ref. 87), 102 (ref. 87), 103 (ref. 28), 110 (refs. 50, 50a), *112*, *114*
Negrini, A., 140 (refs. 42, 43), 141 (refs. 42, 43, 55), 142 (refs. 43, 53–55), 145 (ref. 43), 146 (refs. 42, 43), 153 (ref. 43), 154 (refs. 42, 43), 184 (refs. 42, 43), 185 (ref. 43), *208*, *209*
Neher, H. T., 233 (ref. 55), *257*
Nesmeyanov, A. N., 35 (ref. 46a), *64*, 236 (ref. 190), *260*
Neuberger, A., 218 (ref. 191), *260*
Newman, M. S., 130 (ref. 169), 131 (ref. 168), 151 (refs. 168, 169), 153, 161 (ref. 169), *211*
Newton, L. W., 222 (ref. 147), *259*
Nicholson, A. J. C., 372 (refs. 179, 180), *421*
Nickon, A., 403 (ref. 327), *425*
Nielsen, J. T., 69 (ref. 88), 71 (refs. 87, 89), 72 (ref. 91), 73 (ref. 91), 74 (refs. 12, 87–89), 76 (ref. 91), 77 (ref. 91), 78, 93 (ref. 16), 95 (refs. 89, 90), 96 (refs. 89, 90), 97 (ref. 89), 101 (ref. 87), 102 (refs. 12, 87), *112–114*

Nieuwenhuis, J., 121 (refs. 87, 124, 173), 147 (ref. 69), 155 (ref. 87), 191 (refs. 69, 173), 192 (refs. 124, 173), 193 (ref. 124), 196 (refs. 87, 173), *208–210*, *212*
Nikolić, R., 118 (ref. 3a), 141 (ref. 3a), *206*
Nilsson, W. A., 316 (ref. 92), *327*
Nodzu, R., 217 (ref. 145), *259*
Noffsinger, C. A., 234 (ref. 210), *261*
Nooi, J. R., 123 (ref. 175), 124 (ref. 175), 128 (ref. 175), 129 (refs. 175, 177), 151 (refs. 175, 177), 155 (ref. 177), *212*
Nordlander, J. E., 321 (ref. 108), *328*
Nordt, H., 254, *260*
Normant, H., 1–65, 121 (ref. 29a), 123 (ref. 29a), *207*
Norrish, R. G. W., 372 (ref. 181), 381 (refs. 10, 210), *416*, *421*, *422*
Nothnagel, G., 428, *454*
Novikova, N. V., 35 (ref. 46a), *64*
Nowak, R., 405 (ref. 135), *420*
Noyes, W. A., 368 (ref. 165), 372, 400 (ref. 161), *417*, *419*, *421*
Nudenberg, W., 378 (ref. 146), 381 (ref. 146), 415 (ref. 145), *420*

O

Oehlert, H., 414 (ref. 254), *423*
Offner, A., 246–248 (refs. 154, 155), *259*
Okamoto, Y., 332 (ref. 15), *363*
Oliveri-Mandala, E., 375 (ref. 184), *421*
Olson, A. R., 400 (refs. 185–187), *421*
Omran, S. M. A. E., 374 (ref. 235), 375 (ref. 178), 386 (ref. 178), *421*, *423*
Onsager, L., 307 (ref. 68), *326*
Openshaw, H. T., 432 (ref. 37), *454*
Orchard, W. M., 230 (ref. 49), *256*
Osborn, J. M., 233, *262*
Ostrowski, W., 222 (ref. 249), *262*
Owades, J. L., 414 (ref. 188), *421*
Owen, N. L., 142 (ref. 56), *208*

P

Packard, M. E., 265, 272, *326*
Packard, M. G., 274 (ref. 4), 280 (ref. 4), *325*
Packendorff, K., 233, *260*
Packham, D. I., 340 (ref. 40), *364*
Padgham, D. N., 219 (ref. 194), *261*
Pailer, M., 401 (ref. 189), *421*
Pakhamova, A. P., 236 (ref. 1), *255*
Palchak, J. F., 342 (ref. 52), *364*
Panneman, H. J., 120 (ref. 163), 172 (ref. 163), 174 (ref. 163), *211*
Panouse, J. J., 27 (ref. 67), *64*
Parham, W. E., 199 (ref. 4), 143, 144 (ref. 77), 145 (ref. 4), 146 (refs. 4, 200), 151 (ref. 4), 153–155 (ref. 4), *206*, *209*, *212*, 387 (ref. 318), *425*
Parker, C. O., 401 (ref. 190), *421*
Parker, R. P., 249 (ref. 170), *260*
Parker, S. H., 321 (ref. 110), *328*
Parkes, E. A., 340 (ref. 42), *364*
Pasto, D. J., 399 (ref. 61), *418*
Patat, F., 413 (ref. 153), *420*
Paterno, E., 368, 374 (ref. 193), 379, 390 (ref. 194), *421*, *422*
Patterson, J. M., 373 (ref. 199), *422*
Paul, R., 15 (ref. 68), *64*, 68 (ref. 92), *114*
Pauling, L., 282 (ref. 25), 283 (ref. 25), *325*
Pausacker, K. H., 354 (ref. 96), *365*
Pavlov, V. P., 85, *115*
Pearson, E. G., 400 (ref. 44), *417*
Pelisser, 4 (ref. 25a), *63*
Pelletier, S. W., 400 (ref. 195), *422*
Pengilly, B. W., 415 (ref. 302), *425*
Penner, S. E., 2 (ref. 45), *64*
Perekalin, V. V., 243 (refs. 196, 197), 249, *261*
Perrot, A., 24 (ref. 13), *63*
Peters, F. N., 68 (ref. 34), 99 (ref. 35), 100 (ref. 36), *113*
Petersen, S., 249, *261*
Peterson, D. H., 356 (ref. 104a), *365*
Peterson, J. H., 414 (ref. 170), *421*
Peterson, R. L., 219 (ref. 52), *257*
Petit, A., 404 (ref. 275), *424*
Petrov, A. D., 10, *64*
Petrow, V., 134 (ref. 95), 159 (refs. 91, 95), *209*
Pfeiffer, P., 414 (refs. 196, 197), *422*

Pfleger, R., 232, *261*
Phillips, B., 235 (ref. 201), *261*
Phillips, W. D., 313, 314 (ref. 76), *327*
Piccolini, R., 321 (ref. 110), *328*
Pickles, W., 348 (ref. 76), *365*
Pieck, R., 372 (ref. 198), *422*
Pietra, S., 354 (ref. 95), *365*
Pimentel, G. C., 369 (ref. 206), *422*
Pinkard, H. J., 400 (ref. 298), *424*
Pitts, J. N., 372 (ref. 32), 373 (ref. 199), 380 (ref. 315), *417*, *422*, *425*
Plattner, Pl. A., 134 (ref. 89), 159 (ref. 89), 161 (refs. 89, 106), 162 (ref. 106), *209*, *210*, 337 (ref. 32), *363*
Plieger, P., 177 (ref. 133), *210*
Ploeg, W., 233, *261*
Polya, J. B., 219 (ref. 194), *261*
Ponomarew, A. A., 217 (refs. 203, 204), 218 (ref. 205), *261*
Poos, G. I., 135 (refs. 100a, 100b), 159 (refs. 100a, 100b), 160 (refs. 100a, 100b), *209*
Pople, J. A., 267, 282, 284 (ref. 24), 285, 296 (ref. 36), 302, 304 (ref. 37), 305, 306 (ref. 66), 307, 314 (refs. 66, 85), *325–328*
Porai-Koshits, B. A., 219 (ref. 206), *261*
Porter, G., 369 (ref. 41), *417*
Porter, G. B., 372 (ref. 183), *421*
Poschmann, L., 382 (ref. 56), 383 (ref. 57), 387 (ref. 57), *418*
Postma, J. C. W., 130 (ref. 85), 133 (ref. 85), 158 (refs. 84, 85), 159 (refs. 85, 99a, 99b), 161 (ref. 85), 177 (ref. 84), 182 (refs. 99a, 99b), 197 (refs. 99a, 99b), *209*
Potts, K. T., 69 (ref. 92a), 75, *115*
Pound, R. V., 265, 270 (ref. 45), *326*
Pratt, R. J., 35, *63*
Prelog, V., 77, 104, *115*
Prendergast, M. G., 237 (ref. 88), *258*
Preobrazhenskiĭ, N. A., 85, *115*, 119, 132 (refs. 9, 88), 159 (refs. 88, 154), 160 (ref. 88), 161 (refs. 9, 88), 163 (ref. 9), 200, *207*, *209*, *211*, 247 (refs. 207, 208), 248 (ref. 207), *261*
Preuss, L., 413 (ref. 218), *422*
Price, C. C., 141 (refs. 47, 65, 67), *208*
Pride, E., 130 (ref. 114), 159 (ref. 114), 161 (ref. 114), *210*
Priesing, C. P., 139 (ref. 170), 151 (ref. 170), *212*
Prill, E. J., 220 (ref. 73), *257*
Purcell, E. M., 265, 269 (ref. 44), 270 (ref. 45), 292 (ref. 32), 293 (ref. 32), 296 (ref. 53), *325*, *326*
Puy, C. H. de, 410 (ref. 98), *419*

Q

Quadbeck, G., 215, 218 (ref. 156), 231, *259*, *261*
Quattlebaum, W. M., 234 (ref. 210), *261*
Queck, J., 121 (ref. 160), 122 (ref. 160), 127 (ref. 160), *211*
Quimby, W. C., 389 (ref. 28), *417*
Quinkert, G., 394 (ref. 20), 404 (refs. 132, 133), 415 (ref. 20), *417*, *420*
Quint, F., 414 (ref. 95), *419*

R

Rae, D. S., 353 (ref. 89), *365*
Rainy, W. T., 318 (ref. 100), *327*
Raleigh, D., 68 (ref. 51), 69 (ref. 51), 73, 74 (ref. 51), 80, *113*
Rall, K. B., 243 (refs. 196, 197), *261*
Ramsden, H. E., 2 (ref. 45), 3, 4 (refs. 70a, 70b), 10 (ref. 74), 11 (ref. 75), 38 (ref. 74), 41 (refs. 74, 75), *64*, *65*
Ramsey, N. F., 274, 277, 280 (ref. 31), 286 (ref. 31), 292 (ref. 32), 293 (ref. 32), 296 (refs. 52, 53), 310, 311, *325*, *326*
Raphael, R. A., 26, *64*, 69 (ref. 83a), 71 (ref. 83a), 72 (ref. 83a), 75 (ref. 83a), 81, *114*, 159 (ref. 111), *210*
Rapoport, H., 100 (ref. 95), *115*
Rapp, W., 227 (ref. 125), *259*
Rappen, F., 410 (ref. 168), *421*
Rappoldt, M. P., 404 (refs. 200, 201), *422*
Rassack, R. C., 347 (ref. 68), *364*
Rassoul, A., 374 (ref. 141), *420*
Recktenwald, G., 373 (ref. 199), *422*

Redel, J., 405 (ref. 135), *420*
Reeves, L. W., 280 (refs. 80, 82), 312 (ref. 80), *327*
Reich, 7, *63*
Reichstein, T., 136 (ref. 112), 159 (ref. 112), 161–163 (ref. 112), *210*
Reid, C., 280 (ref. 21), *325*, 371 (ref. 202), 400 (ref. 203), *422*
Reid, E. B., 196 (ref. 146), *211*
Reid, J. D., 217 (ref. 119), *258*
Reid, W., 414 (ref. 204), *422*
Reilly, C. A., 295 (ref. 38), 296 (ref. 38), 300 (ref. 38), 305 (ref. 38), 307 (ref. 38), *326*
Reilly, E. L., 313 (ref. 77), *327*
Reimer, M., 389 (ref. 205), *422*
Reinmuth, O., 4 (ref. 32), 7, *63*
Reiss, W., 196 (ref. 147), *211*
Remers, W. A., 317, *327*
Renz, J., 142 (ref. 58), *208*
Reppe, W., 141 (ref. 62), 182, *208*, *211*
Reusch, W. H., 405 (ref. 4), *416*
Reuter, M., 230 (ref. 211), *261*
Reuther, F. W., 433 (ref. 40), *455*
Reynolds, G. F., 13 (ref. 71a), *64*
Rheiner, A., 142 (ref. 58), *208*, 406 (ref. 91), *419*
Rice, F. O., 217, 229, *261*
Richards, L. M., 353 (ref. 88), *365*
Richards, R. E., 241 (ref. 79), *257*, 314 (ref. 83), *327*
Richter, J. W., 432, 433 (ref. 34), 434 (ref. 34), 436 (ref. 34), *454*
Ridd, J. H., 318 (ref. 101), *327*
Rinehart, K. L., Jr., 316 (ref. 92), *327*
Riniker, J., 400 (ref. 160), *421*
Rintelen, H. v., 410 (ref. 168), *421*
Ripley, R. A., 399 (ref. 306), *425*
Ritchie, P. D., 236 (ref. 3), *255*
Rix, Th. R., 165 (refs. 118, 121), 168 (ref. 127), 179 (ref. 135), 180 (ref. 135), 181 (refs. 136, 137), 182 (ref. 137), 183 (ref. 127), *210*, *211*
Roach, J. R., 224 (ref. 134), 225 (ref. 134), *259*
Roberts, E., 433 (ref. 2), *453*
Roberts, J. D., 127 (ref. 39), 140, *208*, 230 (ref. 218), *261*, 267, 309 (ref. 57), 312, 313 (ref. *79*), 314 (ref. 79), 321 (refs. 108, 110), *326–328*
Robinson, F. M., 135 (ref. 100b), 159 (ref. 100b), 160 (ref. 100b), *209*
Robinson, M., 18 (ref. 72), *65*
Robinson, R., 18 (ref. 72), *65*, 69 (ref. 92a), 75, 81, *115*
Rochow, E. G., 10 (ref. 73), 11 (ref. 76a), 12 (ref. 41), 42 (ref. 41), *63*, *65*, 279, 280 (ref. 12), *325*
Roe, A., 220 (ref. 214), 221 (ref. 214), *261*
Roe, A. S., 216 (ref. 138), 217 (refs. 131, 138), *259*
Roebber, J. L., 369 (ref. 206), *422*
Rogers, M. A. T., 341, *364*
Rogers, M. T., 275 (ref. 20), 280, 314, *325*, 387 (ref. 2), *416*
Rollefson, G. K., 369 (ref. 206), 371 (ref. 207), 400 (ref. 208), *422*
Rosebeek, B., 197 (ref. 174), *212*
Rosen, A. L., 400 (ref. 297), *424*
Rosenberg, S. D., 4 (ref. 70b), 10, 11, 38 (ref. 74), 41 (refs. 74, 75), *64*
Rosenthal, D., 380 (ref. 49), *417*
Ross, J. A., 406 (ref. 310), *425*
Rothlin, E., 83 (ref. 97), *115*
Rout, M. K., 317 (ref. 97), *327*
Rouvé, A., 131 (ref. 107), 161 (ref. 107), 163 (ref. 107), *210*
Rowlinson, H. C., 329
Roy, G. C., 223, *261*
Royer, R., 159 (ref. 91), *209*
Rubtsov, I. A., 85, *115*, 120, 130 (ref. 13), 132 (ref. 88), 133 (ref. 13), 134 (ref. 13), 159 (refs. 13, 88, 154), 160 (ref. 88), 161 (refs. 13, 88), 163 (ref. 13), 189 (ref. 13), 200, *207*, *209*, *211*
Rüegg, R., 121 (ref. 34), 125 (ref. 34), 131–133 (ref. 34), 154 (ref. 34), 158 (ref. 34), 161–163 (ref. 34), *207*
Rummert, G., 200, *211*, 400 (ref. 130), *420*
Rust, F. F., 376 (ref. 110), *419*
Rutgers, J. G., 380 (ref. 315), *425*
Rydon, H. N., 68 (ref. 67), *114*

Ryser, G., 248 (ref. 143), *259*
Rytina, A. N., 334 (ref. 18), *363*

S

Sabanejeff, A., 118, *206*
Sachs, F., 412 (ref. 209), *422*
Sadle, A., 228 (ref. 255), *262*
Sadler, M. S., 280 (ref. 81), *327*
Sadolin & Holmblad, 75 (refs. 9, 10), 76 (ref. 10), 78 (ref. 11), 93 (ref. 16), *112*
Saika, A., 265, 266 (ref. 3), 274 (ref. 3), 275 (ref. 3), 277, 278, 280 (ref. 3), 284 (ref. 3), 293 (ref. 40), 295 (ref. 40), 302 (ref. 40), 304 (ref. 40), 309 (refs. 40, 56), 312, *325–327*
Saito, K., 354 (refs. 98, 99), *365*
Saitow, A., 11 (ref. 76a), *65*
Salemink, C. A., 428 (ref. 30), 431 (ref. 31), 432 (ref. 30), 433 (ref. 30), 434 (refs. 5, 30), 436 (ref. 30), 439 (ref. 30), 444 (refs. 5, 32, 33), 446 (ref. 5), 449 (ref. 30), 453 (ref. 5), *453*, *454*
Saltmarsh, O. D., 381 (ref. 210), *422*
Samokhvalov, G. I., 159 (ref. 154), 200, *211*
Sannie, C., 27 (ref. 67), *64*
Šantavý, F., 398 (ref. 211), *422*
Sarett, L. H., 135 (refs. 100a, 100b), 159 (refs. 100a, 100b), 160, *209*
Saucy, G., 201 (ref. 196), *212*, 248 (ref. 143), *259*
Sauer, J. C., 214 (ref. 120), 215, *258*
Saunders, M., 307 (ref. 68), *326*
Sax, N. W., 246 (refs. 154, 155), 247 (refs. 153–155), 248 (refs. 153–155), *259*
Schäfer, F., 119, 144 (ref. 7), 149 (ref. 7), 150 (ref. 7), 190 (ref. 7), *207*
Schaffner, K., 377 (ref. 325), *425*
Scheibler, H.,118, 141 (ref. 3a), *206*
Schenck, G. O., 232, *261*, 336 (ref. 25), *363*, 369, 374 (ref. 215), 381, 383 (ref. 213), 403 (refs. 212, 326), 408 (ref. 214), *422*, *425*
Scheuchenplug, D. R., 316 (ref. 91), *327*
Schiedt, U., 383 (ref. 57), 387 (ref. 57), *418*
Schindler, O., 136 (ref. 112), 159 (ref. 112), 161–163 (ref. 112), *210*
Schinz, H., 130 (refs. 93, 98), 131 (refs. 94, 96), 132 (ref. 90), 159 (refs. 90, 93, 94, 96, 97), 161 (refs. 90, 94, 97), *209*
Schlientz, W., 415 (ref. 255), *423*
Schlubach, H. H., 380 (ref. 217), *422*
Schmahl, H., 141 (ref. 49), *208*
Schmelzer, H. G., 408 (ref. 321), *425*
Schmetterling, A., 85 (ref. 101), *115*
Schmid, G., 375 (ref. 323), 415 (ref. 323), *425*
Schmid, H., 437 (ref. 21), *454*
Schmidlin, J., 135 (ref. 101), 137 (ref. 101), 159–163 (ref. 101), *209*
Schmidt, C.-H., 68 (ref. 98), *115*
Schmidt, J., 331 (ref. 6), *363*
Schmidt, W., 142 (ref. 59), *208*
Schmidt-Thomé, G. A., 383 (ref. 213), *422*
Schmiedberg, O., 428, 429 (ref. 38), *454*
Schmitz, P., 410 (ref. 1), *416*
Schneider, E., 141 (ref. 48), *208*
Schneider, W. G., 267, 280, 296 (ref. 36), 302, 304 (ref. 37), 305, 306 (ref. 66), 307, 309 (ref. 19), 312 (ref. 80), 314 (refs. 66, 85), *325–328*
Schniepp, L. E., 68 (ref. 51), 69 (ref. 51), 73, 74 (ref. 51), 80, *113*
Schnizer, A. W., 214 (ref. 77), 220 (ref. 217), *257*, *261*
Schönberg, A., 336 (ref. 28), *363*, 368 (ref. 237), 369, 373 (refs. 221, 227), 374 (refs. 220, 222, 232, 235), 375 (ref. 221), 376 (ref. 234), 383 (refs. 219, 227–229, 231–233), 384 (refs. 223, 225, 232), 385 (refs. 224, 230), 386 (refs. 219, 232, 234, 236), 414 (ref. 226), *422–424*
Schöpf, C., 81, 85 (ref. 101), 86, *115*
Schoffler, F., 222 (ref. 249), *262*
Scholl, R., 413 (ref. 218), *422*
Schouten, H., 428 (ref. 30), 431 (ref. 31), 432–434 (ref. 30), 436 (ref. 30), 439 (ref. 30), 449 (ref. 30), *454*
Schreiber, A. J., 27 (ref. 17), *63*
Schulz, W., 87 (ref. 116), *115*

Schulze, F., 9, *63*
Scott, A. I., 382 (ref. 14), *416*
Scott, W. R., 121 (ref. 32), 123 (ref. 35), 129 (ref. 32), 164 (ref. 32), 189 (ref. 32), 193 (ref. 32), 194 (ref. 32), *207*
Searles, S., 164, *210*, 380 (ref. 315), *425*
Secareanu, S., 412 (ref. 238), *423*
Seeles, H., 230 (ref. 172), *260*
Selber, P., 355, *365*
Selby, W., 2 (ref. 22), *63*
Selwitz, C. M., 342 (ref. 52), *364*
Seminow, D. A., 230 (ref. 218), *261*
Sen, S. C., 386 (ref. 241), *423*
Senkus, M., 19, *65*
Senoh, S., 71, *114*
Seyferth, D., 9 (ref. 83), 10–12, 13 (ref. 80), 38 (ref. 78), 41 (ref. 78), 42 (refs. 42, 78, 79, 82, 83), *63*, *65*
Shafiq, M., 394 (refs. 13, 18), 395 (ref. 15), *416*
Shannon, J. S., 336 (ref. 27), *363*
Shapiro, B. L., 287, 291 (ref. 64), *326*
Sharkey, W. H., 319 (ref. 102), *328*
Sharts, C. M., 309 (ref. 57), *326*
Shaver, F. W., 197 (ref. 191), *212*, 236 (ref. 83), 237 (refs. 84, 88, 93, 95, 96, 219), 238 (refs. 89, 90, 92, 97, 98), 239 (refs. 85–87, 91, 92, 99, 100, 220), *257*, *258*, *261*
Shavrygina, O. A., 246 (ref. 187), 247 (ref. 187), *260*
Shaw, B. L., 120 (ref. 17), 122, 127 (refs. 17, 33), 128 (ref. 17), 154 (refs. 17, 33), 164 (ref. 17), 169 (ref. 17), 171 (ref. 17), *207*
Shchukina, M. N., 120, 121 (refs. 23–25), 123 (refs. 23, 25), 127 (refs. 23, 24), 128 (ref. 25), 130 (ref. 13), 133 (ref. 13), 134 (ref. 13), 159 (ref. 13), 161 (ref. 13), 163 (refs. 13, 24, 25), 165 (ref. 24), 172 (refs. 24, 25), 189 (ref. 13), *207*
Sheehan, J. C., 75 (ref. 102), 79, 83, 85, 86, *115*, 174, *210*, *211*, 316 (ref. 94), *327*
Sheppard, N., 309 (ref. 59), 319 (ref. 104), *326*, *328*
Sherman, E., 103, *115*
Shiner, V. J., 240 (ref. 148), *259*
Shokina, V. V., 119, 132 (ref. 9), 161 (ref. 9), 163 (ref. 9), *207*
Shoolery, J. N., 275 (ref. 20), 278, 280, 314, *325*, *327*
Shostakovskii, M. F., 121 (refs. 22, 26), 122 (ref. 38) ,123 (refs. 22, 36,3 8), 127 (refs. 22, 26), 141 (ref. 64), *207*, *208*
Shropshire, E. Y., 142 (ref. 57), *208*
Shtangeev, A. L., 255 (ref. 11), *256*
Shunk, C. H., 317 (ref. 96), *327*, 361, *366*
Sicher, J., 222 (ref. 228), *262*
Sidel'kovskaya, F. P., 121 (ref. 26), 122 (ref. 38), 123 (refs. 36, 38), 127 (ref. 26), *207*, *208*
Sidky, M. M., 386 (ref. 236), *423*
Siebert, E., 143, 144 (ref. 71), 149 (ref. 71), 150 (ref. 71), 164 (ref. 71) 190 (ref. 71), *209*
Siegmann, C. M., 137–139 (ref. 165), 163 (ref. 165), *211*
Siemer, H., 400 (ref. 131), *420*
Sigwart, A., 331 (ref. 6), *363*
Silber, P., 368, 373 (refs. 63, 64, 71, 72, 74), 374 (ref. 73), 381 (refs. 68, 70, 76), 382 (refs. 68, 72, 76), 391 (ref. 69), 401 (ref. 66), 402 (ref. 67), 412, *418*
Silverman, N., 317 (ref. 97), *327*
Simms, J. A., 141 (ref. 63), *208*
Simons, J. K., 347 (ref. 72), *364*
Simons, J. P., 371 (refs. 239), 376 (ref. 239), *423*
Simonsen, J. L., 394 (ref. 240), *423*
Simonyi, I., 82 (ref. 59), 110 (ref. 59), *113*
Sims, A. F. E., 322 (ref. 113), *128*
Sina, A., 374 (ref. 232), 383 (ref. 232), 384 (ref. 232), 386 (ref. 232), *423*
Sinclair, H. K., 319 (ref. 102), *328*
Singh, T., 396 (ref. 291), *424*
Sinnema, Y. A., 161 (ref. 116), 162 (ref. 116), 166 (refs. 116, 123, 125), 167 (refs.1 16, 125), *210*
Sircar, A. C., 386 (ref. 241), *423*

Sixt, J., 229 (ref. 181), *260*
Skattebol, L., 25 (ref. 29), *63*
Skoldnikov, A. P., 219 (ref. 221), *261*
Slavachevskaya, N. M., 249 (ref. 198), *261*
Slichter, C. P., 277, 292 (ref. 33), 296 (refs. 33, 51), 310 (ref. 33), 312, *325*, *326*
Slimmer, M., 118, 121 (ref. 1), 123 (ref. 1), 127 (ref. 1), 153 (ref. 1), 156 (ref. 1), *206*
Slomp, G., 315 (ref. 87), *327*
Smirnova, N. V., 219 (ref. 221), *261*
Smit, V. A., 246 (ref. 189), *260*
Smith, C. W., 230 (ref. 222), *261*
Smith, G., 196 (ref. 145), *211*, 239 (ref. 13), *256*
Smith, H., 130 (ref. 114), 159 (ref. 114) 161 (ref. 114), *210*
Smith, L. I., 192, *210*
Smith, P., 410 (ref. 242), *423*
Smith, P. W. G., 322 (ref. 113), *328*
Smith, S. G., 315, *327*
Smith, W. B., 318 (ref. 100), *327*
Smrt, J., 220 (ref. 225), 221–223, *261*, *262*
Sneeden, R. P. A., 451 (ref. 20), *454*
Snell, R. L., 391 (ref. 87), *418*
Snyder, R. H., 414 (ref. 144), *420*
Soc. Anon. de St. Gobain, 123 (ref. 158), 125 (ref. 158), *211*
Sokolova, T. A., 249 (ref. 174), *260*
Soliman, G., 374 (ref. 141), *420*
Sommelet, 22, *62*
Somokhvalov, G. I., 247 (refs. 207, 208), 248 (ref. 207), *261*
Šorm, F., 220 (ref. 225), 221–223, *261*, *262*
Sorwa, F. J., 168 (ref. 126), *210*
Spence, J. A., 224 (refs. 63, 64), 225, 233 (ref. 65), *257*
Spietschka, E., 407 (refs. 124, 125), 408 (ref. 124), 409 (ref. 127), 410 (ref. 124), *420*
Splitter, J. S., 412 (ref. 244), 414 (ref. 243), *423*
Spoerri, P. E., 401 (ref. 190), *421*
Stacey, F. W., 415 (refs. 270, 271), *424*
Stadler, R., 200 (ref. 153), *211*
Stadtman, E. R., 233 (ref. 229), *262*
Staehelm, A., 387 (ref. 105), *419*
Stampa, G., 415 (ref. 145), *420*
Standke, W., 383 (ref. 149), 387 (ref. 149), *420*
Stanhuis, E. J., 164 (ref. 199), *212*
Stanin, T. E., 235 (ref. 67), *257*
Stankovitch, T. D., 10 (ref. 74), 38 (ref. 74), 41 (ref. 74), *65*
Staudinger, H., 214, 217, 221 (ref. 233), 232, *262*, 396, *423*
Stauffacher, D., 130 (ref. 98), 159 (ref. 98), *209*
Steacie, E. W. R., 372 (ref. 198), *422*
Steadman, T. R., 226 (ref. 234), *262*
Steele, A. B., 253 (ref. 32), *256*
Steele, W. A., 342 (ref. 52), *364*
Stein, G., 406 (ref. 289), *424*
Steinert, R., 339 (ref. 38), *364*
Steinkopf, W., 221 (ref. 235), *262*
Stephens, E., 340 (refs. 42, 44), *364*
Stephenson, O., 121–123 (ref. 128), 127 (ref. 128), *207*
Stern, F., 218, *256*
Stern, K. G., 218 (ref. 236), *262*, 356
Stern, R., 87 (ref. 103a), *115*
Stewart, A. W., 214 (ref. 256), 216 (ref. 256), 220 (ref. 256), *262*
Stewart, F. D., 223, *256*, *262*
Stinivasan, R., 381 (ref. 312), *425*
Stobbe, H., 389 (refs. 247, 248), 401 (ref. 246), *423*
Stockmann, H., 400 (refs. 252, 252a), 415 (ref. 252), *423*
Stöhr, H., 415 (ref. 126), *420*
Stoermer, R., 400 (refs. 249, 250, 252, 252a, 253), 402 (ref. 251), 414 (ref. 254), 415 (ref. 252), *423*
Stoll, A., 78, 79, 82 (ref. 106), 83, 86 (ref. 105), 107, *115*, 142 (ref. 58), *208*, 415 (ref. 255), *423*
Stoll, M., 131 (refs. 107, 108), 161 (refs. 107, 108), 163 (ref. 107), *210*
Stone, B. R., 415 (ref. 281), *424*
Stone, F. G. A., 3 (ref. 1b), 10, 12 (ref.

41), 13 (ref. 1a), 38 (ref. 78), 41 (ref. 78), 42 (refs. 41, 78), *62*, *63*, *65*, 315 (ref. 89), *327*
Stothers, J. B., 371 (ref. 300), 375 (ref. 301), *425*
Stout, G. H., 316, *327*
Strating, J., 119, 144 (ref. 8), 149, 150 (ref. 8), 199, *207*, *209*, *211*
Straub, W., 429 (ref. 39), *454*
Streitwieser, A., 337 (ref. 33), *363*
Stright, P. L., 119 (ref. 4), 143, 145 (ref. 4), 146 (ref. 4), 151 (ref. 4), 153–155 (ref. 4), *206*, 387 (ref. 318), *425*
Stuart, E. R., 395 (ref. 80), *418*
Stuckwisch, C. G., 240 (ref. 22), *256*
Süs, O., 407 (ref. 257), 409 (refs. 257, 259–260), 415 (ref. 258), *423*
Suida, H., 408 (ref. 256), 412 (ref. 256), *423*
Sultanbawa, M. U. S., 142 (ref. 56), *208*
Surmatis, J. D., 246–248 (ref. 155), *259*
Surzur, J. M., 26, 56 (ref. 31), *63*, 201, *211*
Suzuki, T., 354 (ref. 97), *365*
Svetkin, Y. V., 218 (ref. 238), 219, *262*
Swain, G., 345 (ref. 62), *364*
Sweet, A. D., 230, *259*
Sweeting, O. J., 221 (ref. 24), *256*
Symons, M. C. R., 414 (ref. 309), *425*
Szpilfogel, S. A., 137–139 (ref. 165), 163 (ref. 165), *211*

T

Täschler, M., 83 (ref. 97), *115*
Taft, R. W., Jr., 278, *325*
Tamelen, E. E. van, 84, *115*, 323 (ref. 115), *328*, 341 (ref. 48), *364*
Tanasescu, I., 389 (ref. 266), 412 (ref. 263), 413 (refs. 263, 265), 414 (ref. 264), *423*, *424*
Tarbell, D. S., 80, *114*
Taufen, H. J., 241 (ref. 240), *262*
Taylor, A. W. C., 68 (ref. 72), *114*
Taylor, D., 402 (ref. 59), *418*
Taylor, R. P., 373 (ref. 199), *422*
Taylor, W. C., 395 (ref. 17), 398 (ref. 17), *416*
Tchéoufaki, 400, *419*
Teisseire, P., 246, 247, *262*
Templeton, W., 375 (ref. 301), 377 (ref. 166), 378 (ref. 166), 415 (ref. 166), *421*, *425*
Tersarkisyan, G. S., 411 (ref. 162), *421*
Theobald, C. W., 251, *262*
Thiele, J., 334 (ref. 22), 360 (ref. 22), *363*
Thies, H., 433 (ref. 40), *455*
Thiessen, W. E., 399 (ref. 307), *425*
Thoma, R. W., 358 (ref. 111), *366*
Thomas, C. L., 228, 230, *259*
Thompson, D. T., 331 (ref. 12), 332 (ref. 12), *363*
Thompson, H. W., 241 (ref. 245), *262*
Thomson, C. H., 415 (ref. 171), *421*
Tiers, G. V. D., 277 (ref. 48), 287, 291, *326*
Tiffeneau, 2, *65*
Timmons, C. J., 1, 2 (refs. 3, 4), 3 (ref. 3), 35, *62*
Tobinaga, S., 315 (ref. 87), *327*
Tockman, A., 255 (ref. 75), *257*
Todd, A. R., 345 (ref. 62), *364*
Tokar, G., 82 (ref. 59), 110 (ref. 59), *113*
Tolpin, J. G., 329
Torgov, I. V., 27 (ref. 46), 52 (ref. 46), 58 (ref. 46), *64*
Torrey, H. C., 265, *326*
Torto, F. G., 338 (ref. 34), *363*
Tóth, J., 84, *113*
Traube, W., 347 (ref. 73), *365*
Traverso, G., 354 (ref. 95), *365*
Treibs, A., 249 (ref. 246), *262*
Treibs, W., 339, *364*, 387 (ref. 267), *424*
Trenner, N. R., 317 (ref. 96), *327*
Triebsch, W., 144 (ref. 70), 149 (ref. 70), 150 (ref. 7), 190, *209*
Truce, W. E., 119 (ref. 5), 140 (ref. 5), 141 (refs. 5, 61, 63), 142 (ref. 5), 143 (ref. 5), 144, 145–147 (ref. 5), 151 (ref. 5), 153 (ref. 5), 185 (refs. 5, 73), *207–209*
Tse, R. L., 131 (ref. 168), 151 (ref. 168), *211*
Türck, K. H. W., 221 (ref. 233), *262*
Tumanova, Z. M., 236 (ref. 190), *260*
Turner, J. J., 309 (ref. 59), *326*
Turner, R. B., 451 (ref. 20), *454*

Tuttle, W. P., 126 (ref. 40), 127 (ref. 40), 193 (ref. 40), 194 (ref. 40), *208*
Tyle, Z., 71 (refs. 17, 31), 72 (refs. 17, 31, 32), 74 (ref. 31), 90–92 (ref. 17), 101 (ref. 31), 102 (ref. 31), *112*, *113*
Tyler, O., 201 (ref. 196), *212*

U

Ueberwasser, H., 135 (ref. 101), 137 (ref. 101), 159–163 (ref. 101), *209*
Uibrig, Cl., 347 (ref. 71), *364*
Union Oil Co. of California, 141 (ref. 67a), *208*
Uri, N., 414 (ref. 268), *424*
Urry, W. H., 378 (ref. 143), 410 (ref. 269), 415 (refs. 270, 271), *420*, *424*
Urscheler, H., 406 (ref. 91), *419*
Utermohlen, W. P., 234 (ref. 247), 235 (ref. 248), *262*
Utzinger, E., 397 (ref. 272), *424*

V

Van de Vloed, H., 410 (ref. 168), *421*
Van Nes, K., 336 (ref. 29), *363*, 414 (ref. 99), *419*
Van Tamelen, E. E., 394 (ref. 273), *424*
Vegter, J., 123 (ref. 162), 125 (ref. 162), 166 (ref. 183), 202 (ref. 162), *211*, *212*
Veldstra, H., 428 (ref. 29), *454*
Velluz, L., 403 (ref. 276), 404, 405 (ref. 277), *424*
Venketaraman, K., 402 (ref. 278), *424*
Vennesland, B., 356, 357 (ref. 105), *365*, *366*
Verkholetova, G. P., 27 (ref. 46), 52 (ref. 46), 58 (ref. 46), *64*
Verloop, A., 403 (ref. 279), 405 (ref. 121), *419*, *424*
Vernon, C. A., 319 (ref. 106), 320 (ref. 106), *328*
Ver Ploeg, D., 342 (ref. 50), *364*
Viehe, H. G., 144 (ref. 189), 147 (ref. 189), 201 (ref. 189), *212*
Vieregge, H., 120 (ref. 180), 121 (ref. 180), 161 (ref. 180), 175 (refs. 132, 166), 176 (refs. 180, 197), 177 (ref. 180), 178 (ref. 132), *210–212*
Vilkas, M., 18 (ref. 84a), *65*
Vincze, I., 84, *113*
Vinogradov, V. P., 121 (ref. 171), 123 (ref. 171), 124 (ref. 171), 127 (ref. 171), 130 (ref. 171), 131 (ref. 171), 159 (ref. 171), 161 (ref. 171), *212*, 246 (ref. 187), 247 (ref. 187), *260*
Vischer, E., 356 (ref. 104b), 358 (ref. 110), *365*
Vliervoet, J. L. J. van de, 403 (ref. 280), *424*
Vogel, E., 231, *262*
Vogt, I., 414 (ref. 151), *420*
Volcheck, E. J., 100 (ref. 95), *115*
Volger, H. C., 121 (ref. 20), 140 (ref. 20), 141 (ref. 20), 143 (refs. 44, 140), 146 (refs. 20, 44), 147 (ref. 20), 148 (refs. 20, 44), 152 (refs. 83, 140), 154 (ref. 44), 155 (ref. 20), 156 (ref. 20), 159 (refs. 20, 44), 161 (ref. 20), 163 (ref. 20), 183 (ref. 83), 184 (refs. 20, 83, 140, 141), 185 (refs. 83, 140, 141), 186 (refs. 20, 83, 140, 141), 187 (refs. 20, 83, 140), 188 (refs. 20, 140), *207–209*, *211*
Vollema, G., 129 (ref. 178), 147 (ref. 178), 151 (ref. 178), 155 (ref. 178), 185 (ref. 178), *212*
Vollmann, H., 222 (ref. 249), *262*
Vollrath, R. E., 217 (ref. 213), *261*
Vonderwahl, R., 318 (ref. 99), *327*

W

Wagner, E. C., 347 (ref. 69), *364*
Wagner, J. A., 77, *114*
Waidelich, E., 375 (ref. 323), 415 (ref. 323), *425*
Walburn, J. J., 4 (refs. 70a, 70b), 10 (ref. 74), 38 (ref. 74), 41 (ref. 74), *64*, *65*
Walker, J., 68 (ref. 114), *115*
Wall, R. E., 387 (ref. 2), *416*
Walter, J., 299 (ref. 70), *326*
Wang, S. Y., 415 (ref. 281), *424*
Ward, W. R., 251 (ref. 169), *260*
Warren, C. K., 342, *364*
Waser, P. G., 428 (ref. 8), 429 (ref. 8), 431 (ref. 8), 433 (ref. 8), 434 (ref. 8), 436 (ref. 8), 437 (ref. 13), 438 (ref. 13), 442 (ref. 44), 444 (ref. 44), *454*, *455*

Wasserman, H. H., 87 (ref. 103a), *115*, 169 (ref. 172), *212*
Wassermann, A., 241, *262*
Watanabe, Z., 414 (ref. 150), *420*
Waters, C. E., 217 (ref. 213), *261*
Waters, W. A., 383 (ref. 172), 386 (ref. 172), *421*
Waugh, J. S., 283, 304 (ref. 39), 309 (ref. 39), *325*, *326*
Webb, J. S., 93, *115*
Weber, J., 246–248 (ref. 155), *259*
Weedon, B. C. L., 26, *63*, 120, 122 (ref. 15), 130 (ref. 15), 132–134 (ref. 15), 159 (ref. 15), 161 (ref. 15), *207*, 323 (ref. 114), *328*, 338 (ref. 34), 342, *363*, *364*
Wehrli, H., 377 (ref. 325), *425*
Weidlich, H., 87 (ref. 116), *115*
Weiland, J. H. S., 130 (ref. 143), 131 (ref. 143), 159 (ref. 143), 186 (ref. 142), 187 (refs. 142–144), 188 (ref. 144), 189 (ref. 143), *211*
Weinberg, K., 397 (ref. 272), *424*
Weisblat, D. I., 234, *260*
Weiss, F. T., 121 (ref. 21), 123 (ref. 21), 127 (ref. 21), 129 (ref. 21), 130 (ref. 21), 153 (ref. 21), 154 (ref. 21), 157 (ref. 21), 164 (ref. 21), 190, 198 (ref. 21), *207*
Weiss, H. D., 121 (ref. 31), 124, 127 (ref. 31), 129 (ref. 31), 151 (ref. 31), 153 (ref. 31), 155 (ref. 31), *207*
Weizmann, C., 345 (ref. 59), *364*, 373 (ref. 282), *424*
Wells, C. F., 414 (ref. 283), *424*
Wendler, N. L., 373 (ref. 290), *424*
Werber, F. X., 239 (ref. 94), *258*
Werf, S. van der, 165 (ref. 122), 169 (ref. 122), 171 (ref. 122), 191 (ref. 122), *210*
Wertz, J. E., 267, 280 (ref. 17), *325*, *326*
Westerhof, P., 403 (refs. 280, 284), 404 (ref. 200), *422*, *424*
Westheimer, F. H., 356, *366*
Wettstein, A., 135 (ref. 101), 137 (ref. 101), 159–163 (ref. 101), *209*, 356 (ref. 104b), 358 (ref. 110), *365*, 366
Weyenberg, D. R., 9, *65*
Whaley, H. A., 316 (ref. 92), *327*
Whalley, M., 340 (ref. 44), *364*
Wharton, P. S., 169 (ref. 172), *212*
Wheeler, J. W., 395 (ref. 285), *424*
Wheeler, O. H., 131 (ref. 115), 159 (ref. 115), 160 (ref. 115), 161 (ref. 115), *210*, 403 (ref. 40), *417*
Whiffen, D. W., 241 (ref. 245), *262*
Whitcher, W. J., 129 (ref. 41), 156 (ref. 41), 190, *208*
White, A., 218 (ref. 236), *262*
White, R. F. M., 318 (ref. 101), 319 (ref. 106), 320 (ref. 106), *327*, *328*
White, R. W., 322 (ref. 111), *328*, 377 (ref. 86), *418*
Whitham, G. H., 340 (ref. 43), *364*, 392 (ref. 308), *425*
Whiting, K. D. E., 350 (ref. 86), 354, *365*
Whiting, M. C., 25 (ref. 29), *63*, 120 (ref. 17), 122, 127 (refs. 17, 33), 128 (ref. 17), 154 (refs. 17, 33), 164 (ref. 17), 169 (ref. 17), 171 (ref. 17), *207*
Whitman, D., 307 (ref. 68), *326*
Wiberg, K. B., 6, *65*, 407 (ref. 286), 408 (ref. 286), *424*
Wiegand, C., 402 (ref. 287), *424*
Wiegman, A. M., 140 (refs. 182, 184), 141 (ref. 182), 145 (ref. 182), 146 (refs. 182, 184), 147 (refs. 182, 184), 151 (refs. 182, 184), 164 (ref. 182), 184 (ref. 182), 186 (ref. 182), *212*
Wieland, P., 77, 104, *115*, 135 (ref. 101), 137 (ref. 101), 159–163 (ref. 101), *209*
Wiggenink, G. L., 415 (ref. 138), *420*
Wilbert, G., 231, *256*
Wilds, A. L., 330 (ref. 2), 361, *363*, *366*
Wiley, R. H., 319 (ref. 105), *328*, 394 (ref. 103), *419*
Wilk, M., 414 (ref. 204), *422*
Wilkinson, S., 432 (ref. 37), *454*
Willhalm, B., 131 (ref. 108), 161 (ref. 108), *210*
Williams, C. J., 102, 106, *112*
Williams, G. A., 241 (ref. 10), *256*, 293 (ref. 40), 295 (ref. 40), 302 (ref. 40), 304 (ref. 40), 309 (ref. 40), *326*
Williams, H., 93, *115*
Williams, J. W., 216 (refs. 251, 252), 217, 228 (refs. 141, 255), 229 (ref.

253), 230 (ref. 141), 233, 240, *259*, *262*
Williams, R. B., 273, 318 (ref. 99), *326*, *327*
Williams, R. W. J., 404 (ref. 60), *418*
Wilsmore, N. T. M., 214, 216, 217, 220 (refs. 256, 257), 221 (ref. 60), 222, 229, 240, 241 (ref. 258), 242, 248, 249 (ref. 259), 252, 253 (ref. 258), *262*, *263*
Wilson, C. L., 102, 106, *112*
Wilson, C. V., 360, *366*
Wilson, W., 68 (ref. 118), *115*
Windaus, A., 406 (ref. 289), 414 (ref. 288), *424*
Winstein, S., 315, *327*
Wirtz, P., 408 (ref. 328), *425*
Wisaksono, W., 162 (ref. 190), *212*
Witford, W. R., 4 (ref. 70a), *64*
Witkop, B., 314 (ref. 86), *327*
Witt, H., 2 (ref. 87a), *65*
Witte, H., 141 (ref. 49), *208*
Witte, K., 375 (ref. 323), 415 (ref. 323), *425*
Wittig, G., 2 (refs. 87a, 87b), *65*
Wohl, A., 80, *115*
Wolf, B., 248 (ref. 185), *260*
Wolf, D. E., 317 (ref. 96), *327*
Wolf, R., 382 (ref. 303), *425*
Wolfe, J. R., 387 (ref. 114), *419*
Wolff, A., 382 (ref. 56), *418*
Wolinsky, J., 323 (ref. 115), *328*, 394 (ref. 273), *424*
Wollenberg, O., 219 (ref. 261), *263*
Wolovsky, R., 402 (ref. 109), *419*
Woodward, R. B., 196 (ref. 145), *211*, 373 (ref. 290), 395 (ref. 299), 396 (ref. 291), *424*, *425*
Wooldridge, K. R., 342 (ref. 53), 350 (refs. 85, 87) 351, *364*, *365*
Woolley, B. L., 230 (ref. 81), *257*
Wright, G. F., 230 (refs. 49, 81), *257*
Wright, J. R., 7, *63*
Wyman, G. M., 400 (refs. 43, 44, 292), *417*, *424*
Wynberg, H., 341 (ref. 46), 342 (ref. 50), *364*

X

Xuong, Ng. D., 342 (ref. 51), *364*

Y

Yang, D-D. H., 375 (ref. 293), 376, *424*
Yang, N. C., 82 (ref. 85), *114*, 375 (ref. 293), 376, 377 (refs. 12, 325), 393 (ref. 48), *416*, *417*, *424*, *425*
Yankwich, P. E., 241 (ref. 10), *256*
Yanovskaya, L. A., 246 (refs. 188, 189), 247 (refs. 188, 189), 248 (ref. 188), *260*
Yarnold, E. T., 414 (ref. 38), *417*
Yates, P., 316, *327*, 389 (ref. 294), 390 (ref. 294), 416 (ref. 294), *424*
Yoshida, M., 382 (ref. 134), *420*
Young, F. G., 224 (refs. 262, 263), 226 (ref. 265), 227 (ref. 264), 236 (ref. 33), *256*, *263*
Yufit, S. S., 246 (ref. 189), *260*
Yur'ev, 100

Z

Zaugg, H. E., 215, 226 (ref. 266), *263*
Zavarin, E., 387 (ref. 295), *424*
Zechmeister, L., 400 (refs. 297, 298), 402 (refs. 89, 159, 296), *419*, *421*, *424*
Zeile, K., 75 (ref. 123), 77, 86 (ref. 121), 87, 88 (ref. 121), 89 (refs. 65, 122), *114*, *115*
Zeiser, H., 347 (ref. 64), *364*
Zelinsky, N. D., 233 (ref. 193), *260*, 349 (ref. 78), *365*
Zeller, P., 121 (ref. 34), 125 (ref. 34), 131–133 (ref. 34), 154 (ref. 34), 158 (ref. 34), 161–163 (ref. 34), *207*, 442–444 (ref. 3), *453*
Ziegler, H., 383 (ref. 122), 384 (ref. 122), 403 (ref. 326), 408 (ref. 214), *420*, *422*, *425*
Ziegler, K., 1 (ref. 88), *65*, 347 (ref. 64), *364*
Zimmerman, J. R., 275 (ref. 49), *326*
Zoellner, E. A., 2 (ref. 22), 7 (ref. 21), *63*
Zwanenburg, B. G., 127 (ref. 193), 128 (ref. 193), 146 (ref. 193), 169 (ref. 193), *212*
Zwicky, G., 442 (ref. 44), 444 (ref. 44), *455*

SUBJECT INDEX*

A

Absorption signal, 272
Acepleiadylene, nuclear magnetic resonance spectrum, 314
Acetaldehyde, photochemical reaction, 386
Acetals, reaction with ketene, 223
  unsaturated, preparation, 48
Acetamides, nitrogen-substituted, 181
Acetates, preparation with isopropenyl acetate, 233
Acetoacetates, acetylenic, pyrolysis, 247
  preparation with diketene, 242
  unsaturated, pyrolysis, 244
Acetoacetic esters (*see also* Ethyl acetoacetate), 242
Acetoacetyl chloride, 253
Acetone, irradiation, 374
  as solvent in irradiation, 375
Acetonylacetone, reaction with ketene, 225, 227
Acetophenone, irradiation, 374
2-Acetoxyfuran, 106
6-Acetoxy-3,6-heptadienoic acid, preparation, *415*
Acetylacetone, *C*-acylation with ketene, 233
  reaction with isopropenyl acetate, 234
  reaction with ketene, 225, 227
  by rearrangement, 235
Acetylation, with ketene, 225, 233, 234
Acetyl chloride, from ketene, 220
α-Acetyl-δ-chloro-γ-valerolactone, preparation, 444
Acetylcholine, 428
3-Acetyl-2,4-dihydroxyquinoline, 250
Acetylenemagnesium bromide, preparation, 25
Acetylenes (*see also* Triple bond), irradiation, 401
  photochemical addition of carbonyl compounds to, 380
Acetylenic hydrogens, and chemical shifts, 284, 290
2-Acetylfuran, conversion into 2-methyl-3-pyridinol, 92
Acetyl radicals, 372
Acetylsulfoacetic acid, from ketene, 229
α-Acetyltetramic acids, 250
α-Acetyltetronic acids, 243
Acid anhydrides (*see also* Anhydrides), preparation with ethoxyethyne, 169, *206*
  reaction with alkenylmagnesium halides, 29
Acid azides, 410
Acid chlorides, reactions, with alkenylmagnesium halides *38*
  with ketene, 221
Acids, cyclic hydroxamic, 95
  β-hydroxy, amides of, 183
  reactions, with isopropenyl acetate, 235
  with β-propiolactone, 239
  α,β-unsaturated, preparation, 35, 62
Acrolein, reaction with ketene, 228
Acrylic acid, by depolymerization, 236
Acrylic esters, 237
Activation energies, 312
C-Acylation, with diketene, 255
  with ketene, 233
Acyloins, 242
Addition, of hypohalogen acids to dihydrofurans, 79
1,4-Addition of vinylmagnesium bromide, 35
Adsorption chromatography, and separation of diastereoisomers, 450

*Italic numbers refer to experimental procedures.

β-Alanine, from β-propiolactone, 238
Alcohols, dehydrogenation, 354
β-ethylenic, preparation, 18
reaction with isopropenyl acetate, 233
α,β-unsaturated, preparation, 20, 25, 48
Aldehydes, dialkylamino, reaction with alkenylmagnesium halides, 24
enol acetylation, with ketene, 225
with isopropenyl acetate, 234
α-halogeno, reaction with alkenylmagnesium halides, 23
β-lactones from, 226
reactions, with allylic hydrogen, 375
with alkenylmagnesium halides, 20
α,β-unsaturated, from alkoxyethynylcarbinols, 161
from chloroethynylcarbinols, 201
from ethoxyethynylcarbinols, 167
preparation, 23, 30
reaction with alkenylmagnesium halides, 25
reaction with ketene, 227
Aldols, acetoacetates of, 242
Alkaloids, 427
Alkenes, photochemical reaction with oxygen, 403
Alkenyl borates, 13
Alkenyllithium compounds, 2
Alkoxyalkynes, reactions, with alcohol, 183
with amines, 179
with carbenes, 179
with ethanethiol, 183
with hydroxylic acids, 168
with water, 183
reduction, 189
Alkoxydienes, from alkenylmagnesium halides, 15
1-Alkoxy-2-ethylthioethene, addition of ethaneselenol, 186
Alkoxyethynes, stability of, 126
use in preparation of peptides, 172
Alkoxyethynylcarbinols, preparation, 157
rearrangement, 159, 160
tables of, 130–139
α-Alkoxy ketones, reaction with alkenylmagnesium halides, 22
6-Alkoxytropinones, 83
(α-Alkoxyvinyl)dialkylamines, 179
Alkylation, with β-propiolactone, 239
Alkyl borates, 13
Alkyl nitrites, rotational barrier in, 313
(Alkylthio)ethynylcarbinols, conversion into α,β-unsaturated aldehydes, 163
preparation, 159
rearrangement, 161
S-Alkylthioureas, reaction with diketene, 250
Alkylvinyltins, action of stannic chloride on, 10
Alkynyl ethers, pyrolysis, 196
Alkynyllithium compounds, 2
Alkynylorganometallic compounds, from alkenyl halides, 2
Alkynyl thioethers, *see* Ethynyl thioethers
Allenyl ethers, 124
isomerization into propargyl ethers, 125
Allomuscarine, 440
Allylic alcohols, dehydrogenation, 342
Allylic halides, reaction with alkenylmagnesium halides, 16
Allylic protons, and nuclear magnetic resonance spectra, 285
Allylic radicals, by irradiation, 375
Allylmagnesium bromide, nuclear magnetic resonance spectrum of, 321
Aluminum hydride, and tetrahydrofuran, 6
Amarine, 340
Amides, from alkoxyethynes, 172
of β-hydroxy acid, 183
reaction with alkenylmagnesium halides, 32
Amidines, 180
reaction with diketene, 250
Amines, reactions, with diketene, 248
with isopropenyl acetate, 234

Amines (*continued*)
unsaturated, preparation, 18, 19, 37, 49
Amino acids, from furfuryl amine, 81, 82
Amino aldehydes, reaction with alkenylmagnesium halides, 24
β-Amino esters, from ethoxyethyne, 177
reaction with diketene, 249
Amino ketones, reaction with alkenylmagnesium halides, 24
Ammonia, liquid, purification, 154
Amylsodium, 2
Androsterone, irradiation, 382
Anhydrides (*see also* Acid anhydrides), reaction with isopropenyl acetate, 235
Anilides, formation, 35
Anisaldehyde, irradiation, 374
Anthracene-9-aldehyde, photodimer of, 387
Anthracene-9-carboxylic acid anhydride, photodimer of, 387
Antimony, organic compounds of, 12
Apparatus, for electrolytic alkoxylation, 108
for irradiation, 369
Aromatic protons, and chemical shifts, 282, 291
Aromatic systems, irradiation, 407
Aromatization, *see* Dehydrogenation
Aroyl acrylic acids, isomerization, 400
Arsenic, organic compounds of, 12
3-Aryl-5-isoxazolone, 195
Aspidospermine, nuclear magnetic resonance spectrum of, 317, 283
Axial protons, and nuclear magnetic resonance spectra, 314
Azaazulenes, formation by dehydrogenation, 339
Azides, irradiation, 408
1-Azido-1-ethoxyethene, 166
Azobenzene, reaction with α-diazodeoxybenzoin, 408
cis-Azobenzene, photochemical formation, 402
reaction with ketene, 232
cis-2,2′-Azonaphthalene, 402
cis-2,2′-Azopyridine, 402
Azoxybenzene, photochemical rearrangement to *o*-hydroxyazobenzene, 412
Azulene, nuclear magnetic resonance spectrum of, 314

B

Bacteriochlorophyll, 340
Benzaldehyde, irradiation, 374
Benzene, irradiation, 407
in presence of maleic anhydride, 407
photochemical reaction with diazo esters, 408
Benzenoid compounds, from furans, 97
Benzhydryl phenyl ketone, nuclear magnetic resonance spectrum of, 318
Benzil, 383
Benzocycloheptene, dehydrogenation, 337
Benzoheptindole, dehydrogenation, 339
Benzophenone, irradiation, 374
p-Benzoquinone (*see also* Quinones), photochemical reaction, 387
Benzoquinone adducts, with cyclooctatetraene, irradiation, 391
with cyclopentadiene, 391
Benzoquinones, photodimerization, 390
(Benzoylthio)acetaldehyde, 188
Benzylamine, as hydrogen acceptor, 347
Benzylic alcohols, dehydrogenation, 342
Benzylic hydrogens, and nuclear magnetic resonance spectra, 284
Benzylideneaniline, reaction with ketene, 232
Benzyl ketones, irradiation, 375
N-Benzyloxycarbonyl-*S*-benzyl-*L*-cysteinyl-*L*-tyrosine, preparation, *205*
Betaines, from β-propiolactone, 238
Biochemical hydrogen transfer, 356
1,2-Bisalkylthioethenes, from dichloroethene, 144

1,2-Bisalkylthioethynes, 186
1,2-Bisarylthioethers, from dichloroethene, 144
Bis(arylthio)ethynes, bromine addition to, 190
  hydration, 164
1,2-Bis-*tert*-butylsulfonylethyne, 199
1,2-Bis(*tert*-butylthio)ethyne, from trichloroethene, 149
1,3-Bisisopropylidenecyclobutane-2,4-dione, 197
Boron, organic compounds of, 13
Boron fluoride, 176
Bromoacetone, 253
Bromoacetyl bromide, from ketene, 220
2-Bromoallyl bromide, 17
1-Bromo-2-chloroethane, 307, 314
Bromocresol green, 433
2-Bromopenta-1,4-diene, 17
1-Bromo-2-phenoxyethyne, 118, 156
Buchner acids, nuclear magnetic resonance spectra of, 318
Butadiene, reaction with ketene, 231
1,4-Butanediol, 73
Butane-1,2,3,4-tetracarboxylic acid, ethyl ester, 171
Butene-1, metallation, 2
Butoxyethyne, 184
1-*tert*-Butylthio-1,2-dichloroethane, 149
Butynedioic acid, reaction with ethoxyethyne, 171
β-Butyrolactone, 240
  from diketene, 252

C

Cafestol, nuclear magnetic resonance spectrum of, 315
Camphor, irradiation, 381
  nuclear magnetic resonance spectra of derivatives, 314
Canizzaro reaction, influence of light, 414
ω-Caprolactone, from ketene, 224
Carane, photochemical synthesis, 410
Carbenes, from diazoalkanes, 410
  from diazo ketones, 407
Carbodiimides, reaction with diketene, 251
2-Carbomethoxyfurans, 93
2-Carbomethoxy-5-isopropylfuran, 94
1-Carbomethoxytropinone, 89
Carbon dioxide, reaction with alkenylmagnesium halides, 35
Carbonium ions, as hydrogen acceptors, 348
Carbon-nitrogen double bonds, isomerization, 402
Carbon-oxygen bond, rupture, 17
Carbon tetrachloride, as dehydrogenation promotor, 353
Carbonyl compounds, reaction with alkoxyalkynes, 174
  α,β-unsaturated, photochemical reactions, 387
Carboxylic acids, *see* Acids
1-Carboxytropinone, 89
Carene, photochemical synthesis, 410
Carene oxide, *see* Chrysanthenone
cis-β-Carotene, isomerization, 400
trans-β-Carotene, 400
Carvone camphor, 391
Catalytic hydrogen transfer, 349
Cell, for electrolytic alkoxylation, 108
Charge transfer complex, 331
Chelates, and proton resonance, 280
Chemical exchange, deuterium, in glyoxaline, 318
Chemical shift, 273, 274
  and aromatic protons, 282
  configurational effects, 280
  and ethylenic protons, 282
  Hammett's constants, 278
  standardized values, 287
Chitaric acid, preparation, 441
  starting material for muscarine synthesis, 441
Chloral, reaction with alkenylmagnesium halides, 24
Chloranil, dehydrogenation with, 332
Chlorine radical, 375
Chloroacetal, 125
Chloroacetone, 253
Chloroacetyl chloride, from ketene, 219

Chloroalkyl ethers, reaction with ketene, 221
1-Chloro-1-(ethylthio)ethene, 165
Chloroethynylcarbinols, conversion into α,β-unsaturated aldehydes, 201
from dichloroethyne, 201
Chlorohydrins, unsaturated, 23
trans-β-Chlorovinyl(*p*-nitrophenyl) thio ether, 141
3,5-Cholestadiene, irradiation, 406
Choline, 428
Chromate oxidation, photochemically induced, 414
Chrysanthenone, from verbenone, 392
Cinnamaldehyde, azine, isomerization, 402
Cinnamic acids, photodimerization, 388, 389
photoisomerization, 400
"*Cis*" effect, 319, 320
Citral, synthesis, 120
Colchicine, irradiation, 398
Columbin, nuclear magnetic resonance spectrum of, 315
Combination lines, 304
Conformation, relation to chemical shift, 286
Conformational changes, kinetics of, 312
Coumarin, photodimerization, 387
Coupling constants, 295
Cross-conjugated homoannular dienones, irradiation, 394
Crotonaldehyde, reaction with ketene, 237
Cuprous ethoxyethynylide, 153
Cyanoacetamide, reaction with β-propiolactone, 238
4-Cyano-1,2-naphthaquinone, photochemical reaction with acetaldehyde, 386
Cyclobutane, from photolysis, 372
Cyclobutanedione, 196
Cyclobutanone, from ketene, 230
Cyclobutenone ethers, reactions involving the ether group, 195
transformation into naphthols, 193
Cyclodecanone, irradiation, 377
Cyclodehydrogenation, 347
2,4-Cycloheptadienone, dehydrogenation of, 341
Cycloheptatrienecarboxylic acids, nuclear magnetic resonance spectra of, 317
Cyclohexadiene, irradiation, 403
reaction with ketene, 231
1,3-Cyclohexadienes, dehydrogenation, 336
Cyclohexane, nuclear magnetic resonance spectrum of, 314
Cyclohexanone, as hydrogen acceptor, 354
nuclear magnetic resonance spectrum of, 314
photochemical hydrolytic cleavage, 382
Cyclohexene, irradiation, 375
thermal stability, 349
cis-Δ^4-Cyclohexene-1,2-dicarboxylic acid, dehydrogenation, 354
Δ^2-Cyclohexenyldimethylcarbinol, preparation, *415*
Cyclohexenyllithium compounds, 3
Cyclohexylideneacetaldehyde, preparation, *204*
Cyclooctanone, irradiation, 377
Cyclooctatetraene, adduct with benzoquinone, irradiation, 391
complex with iron pentacarbonyl, nuclear magnetic resonance spectrum of, 315
Cyclopentadiene, adducts, with benzoquinone, irradiation, 391
with tetrafluoroethylene, nuclear magnetic resonance spectrum of, 318
reaction with ketene, 231
Cyclopentanone, photolysis, 372
Cyclopropanone, from ketene, 230
3,5-Cyclosteroids, by irradiation, 406

D

Dammarenolic acid, 382

Decalin, distinction of *cis* and *trans* forms, 314
Decarboxylative dehydrogenation, 345
Dehydroacetic acid, by dimerization of diketene, 253
Dehydroergosterol, irradiation, 406
Dehydrogenases, 356, 357, 358
Dehydrogenation, 329 ff.
  photochemically induced, 414
  ring size and, 337
Dehydrolinaloöl acetoacetate, pyrolysis, 248
7-Dehydro-19-norcholesterol, 405
Dehydrophotosantonic acid, nuclear magnetic resonance spectrum of, 323
Δ^6-Dehydroprednisolone acetate, formation by dehydrogenation, 344
D-3-Desoxyallosaminic acid, 442
Desoxybenzoin, irradiation, 373, 374
Desoxyscopoline, 86
Deuterated ketones, photolysis, 372
Deuterium exchange in glyoxaline, 318
2,5-Diacetoxy-3-chloro-4-hydroxytetrahydrofuran, 107
2,5-Diacetoxy-2,5-dihydrofuran, preparation, *111*
  pyrolysis, 106
Diacetyl, end acetylation, with isopropenyl acetate, 234
  with ketene, 225, 227
Diacetylene, 200
Diacetyl peroxide, from hydrogen peroxide, 216
2,5-Diacyloxy-2,5-dihydrofurans, *cis-trans*, 104
  hydrolysis, 105
  preparation, 103
  reactions, 105
2,5-Dialkoxy-2,5-dihydrofurans, hydrolysis, 80
  potential applications, 103
  preparation, 68
  pyrolysis, 102
  reactions, 72
2,5-Dialkoxy-3-halogeno-4-hydroxytetrahydrofurans, preparation, 79
2,5-Dialkoxytetrahydrofurans, hydrolysis, 80
  preparation, 73
p,p'-Dianisil, 383
Diarylvinyl halides, reaction with magnesium, 1
Diastereoisomers, separation, 450
1,1-Diazido-1-ethoxyethane, reaction with hydrazoic acid, 167
Diazoalkanes, photochemical decomposition, 410
  reaction with benzene, 410
α-Diazodeoxybenzoin, reaction with azobenzene, 408
Diazomethyl *tert*-butyl ketone, 408
Diazonium salts, photochemical decomposition, 415
Dibenzalsuccinic anhydrides, photochemical cyclization, 401
Dibenzyl, dehydrogenation, 338
  formation by irradiation, 374
Dibromides, conversion into ethynyl thioethers, 142
1,2-Dibromo-2-methylpropane, 314
2,3-Dibromo-2-methylpropionic ester, 314
2,4-Dicarbomethoxytropinone, 89
1,4-Dicarbonyl compounds, intermolecular condensations, 81
  intramolecular condensations, 90
Dichloroacetyl chloride, from ketene 219
2,4-Dichloroaniline, nuclear magnetic resonance spectrum of, 304
2,5-Dichloroaniline, nuclear magnetic resonance spectrum of, 304
1,2-Dichlorobenzene, nuclear magnetic resonance spectrum of, 307
p,p'-Dichlorobenzophenone, irradiation, 374
1,4-Dichlorobut-2-yne, 200
Dichlorocarbene, reaction with alkynyl ethers, 178
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, 336
  preparation, *360*

Dichloroethene, conversion into 1,2-bis-alkyl(or aryl)thioethers, 144
isomerization, 400
1,1-Dicyclohexenyl, 345
Diels-Alder reactions, of quinones, 334
with β-propiolactone, 239
Dienes, from alkenylmagnesium halides, 14, 15, 16
preparation, 47
Dienols, from alkenylmagnesium halides, 15, 16
Dienone-phenol rearrangement, photochemically induced, 396
Dienones, photodimerization, 390
preparation, 27, 57
1,3-Diethoxybut-3-en-1-yne, 194
Diethyl 1,4-dihydro-1,2,6-trimethylpyridine-3,5-dicarboxylate, nuclear magnetic resonance spectrum of, 322
Diethyldivinylgermane, preparation, 12
Diethyl fumarate, 442
Diethyl ketone, as solvent in irradiation, 375
Diethyl maleate, 442
Diethyl malonate, reaction with β-propiolactone, 238
1,1-Difluoroethylene, coupling constants of, 295
nuclear magnetic resonance spectrum of, 307
Dihydroacridines, dehydrogenation, 340
1,4-Dihydrobenzenes, 346
1,2-Dihydrocarbazole, dehydrogenation, 331
Dihydrofuranones, 446
3,4-Dihydroisoquinoline, formation by dehydrogenation, 340
Dihydrolimonene, formation of allylic radical by irradiation, 375
Dihydronaphthalenes, dehydrogenation, 332, 337
Dihydro-1,3-oxazines, 250
Dihydrophenanthridines, dehydrogenation, 340
2,5-Dihydro-3-phenylfuran, dehydrogenation, 341
Dihydropyridines, dehydrogenation, 340
Dihydroquinolines, dehydrogenation, 340, 347
Dihydrothiophenes, dehydrogenation, 342
2,3-Dihydroxybenzoic acid, from methyl furoate, 97
1,5-Dihydroxy-6-cyclohexyl-2-pyridone, 95
cis-3,4-Dihydroxy-2,5-dialkoxytetrahydrofurans, preparation, 75
1,5-Dihydroxy-6-(*n*-hexyl)-2-pyridone, 95
α,α′-Dihydroxyketones, from ethoxyethynylcarbinols, 188
1,5-Dihydroxy-6-methyl-2-pyridone, 95
1,5-Dihydroxy-2-pyridone, 96
cis-6,7-Dihydroxytropinone, 86
d,l-trans-6,7-Dihydroxytropinone, 87
α,β-Dihydroxyvaleric acid, 435
Diketene, acidity of, 241
C-acylation with, 252
bromination, 252
chlorination, 252
constitution of, 240
hydrogenation, 240, 252
"ketone" adduct, 255
ozonolysis, 240, 241
preparation, 229
pyrolysis, 241
reactions, with acids, 252
with aldehydes, 254
with amines, 248
with alcohols, 242
with hydrogen chloride, 253
with ketones, 254
with phenols, 243
with thiols, 251
with urea derivatives, 250
with water, 241
α-Diketones, nonenolizable, addition of olefins to, 383
irradiation, 383

1,3-Diketones, reaction with alkenylmagnesium halides, 27
β-Diketones, reaction with β-propiolactone, 238
Dimerization, of diketene, 253
photochemical, 387
p,p'-Dimethoxybenzophenone, irradiation, 374
2,5-Dimethoxy-2,5-dihydrofurans, *cis-trans* isomerism, 72, 76
preparation, *107*
2,5-Dimethoxy-2,5-dihydrofurfural, 96
2,5-Dimethoxy-3,4-oxidotetrahydrofuran, 85
2,5-Dimethoxytetrahydrofuran, *cis-trans* isomerism, 73
preparation, *110*
cis-6,7-Dimethoxytropinone, 86
Dimethyl citraconate, nuclear magnetic resonance spectrum of, 319
1,3-Dimethylenecyclobutane, nuclear magnetic resonance spectrum of, 321
Dimethylformamide, rotational barrier in, 313
Dimethyl fumarate, nuclear magnetic resonance spectrum of. 319
2,2-Dimethylindane, dehydrogenation, 338
Dimethyl 3-ketopentadienedicarboxylate, photodimerization, 390
Dimethyl maleate, nuclear magnetic resonance spectrum of, 319
Dimethyl mesaconate, nuclear magnetic resonance spectrum of, 319
1,2-Dimethylnaphthalene, formation by dehydrogenation, 337
Dimethylnitrosamine, rotational barrier in, 313
2,6-Dimethylpyrone, 253
photodimerization, 388, 390
preparation, *416*
2,6-Dimethyl-γ-pyrone-3-carboxylates, 244
Dimethyl sulfide, reaction with β-propiolactone, 239
Dimethyl sulfoxide adducts, nuclear magnetic resonance spectrum of, 315
1,1-Dimethyltetralin, dehydrogenation, 337, 353
Di-α-naphthyl ketone, irradiation, 374
2,7-Dinitrophenanthraquinone, in dehydrogenation, 336
C^{13}-Dioxane, 309
Dipeptide, preparation, *205*
Diphenyl, as dehydrogenation promotor, 353
Diphenylacetylene, irradiation, 401
Diphenylbutatriene, isomerization, 400
1,2-Diphenyl-3,4-dimethylenecyclobutene, 315
Diphenylketene, 192
Diphenyloctatetraene, isomerization, 400
Diphosphopyridine nucleotide, 356
Dipropyl ketone, as solvent in irradiation, 375
Direct dipolar coupling, 292
Dispersion mode, 273
Disulfides, as hydrogen acceptors, 347
Double coil nuclear induction method, 272
Dragendorff's reagent, 433

E

Einstein's law of photochemical equivalence, 371
Electrolysis, of furan, *107*
Electrolytic methoxylation, 71
Electronegativity, and chemical shift, 277
Electron spin density 293
Electrophilic reagents, additions to the triple bond of ethynyl ethers and thioethers, 163
Enamines, 185
Enol acetates, preparation, with isopropenyl acetate, 234
with ketene, 224–225
Enol acetylation, of aldehydes, 234
with ketene, 224
of aldehydes, 225
of α,β-unsaturated aldehydes, 226

Enol acetylation (*continued*)
of α,β-unsaturated ketones, 224
of ketones, 234
Epiallomuscarine, 440
Epichlorohydrin, reactions, with ethoxyethynyllithium, 155
with (ethylthio)ethynyllithium, 155
with sodioacetic ester, 444
Epimuscarine, 440
1,2-Epoxides, reaction with alkenylmagnesium halides, 18
Equatorial protons, and nuclear magnetic resonance spectra, 314
Ergosterol, 404
Esterification, by alkoxyethynes, 172
Esters, β-amino, 177
diazo, irradiation, 408
hydroxy, acetoacetates of, 243
β-hydroxy, 160
isopropenyl, 235
β-keto, reaction with β-propiolactone, 238
reaction with alkenylmagnesium halides, 28
thiol, α,β-unsaturated, from (alkylthio)ethynylcarbinols, 161
α,β-unsaturated, from alkoxyethynylcarbinols, 159
from ethynyl ethers, 176
nuclear magnetic resonance spectra of, 319, 320
Ethanes, rotational barriers in, 313
Ethanol, nuclear magnetic resonance spectrum of, 292
(−)-Ethanol-1-*d*, synthesis, 356
Ethers (*see also* under Ethynyl, Ethynylene), dialkylamino, reaction with alkenylmagnesium halides, 18
diazido, 166
α,α-dihalogeno, 165
α,β-dihalogeno, reaction with alkenylmagnesium halides, 14
α-ethylenic, preparation, 14
α-halogeno, reaction with alkenylmagnesium halides, 14, 43
β-halogenovinyl, interconversion of *cis* and *trans* isomers, 125
β-halogenovinyl alkyl, preparation, 122, 123
β-halogenovinyl aryl, preparation, 122
γ-hydroxy, 189
imino, 180
ortho, 168
Ethoxyalkynes, formation of amides with, 197
formation of β-lactams with, 198
reactions involving the ether group, 195
1-Ethoxybut-1-ene-3-yne, 200
2-Ethoxybut-1-ene-3-yne, 200
Ethoxybutyne, reaction with hydrogen chloride, 172
1-Ethoxy-1,2-(diethylthio)ethane, 183
1-Ethoxy-2-(ethylthio)ethene, conversion to ethyleneethyne, 143
Ethoxyethyne, additions to, of alcohols, 167
of halides, 165
of hydrazoic acid, 164
of phenols, 167
attempted Mannich reaction, 157
attempted oxidative coupling, 157
conversion to β-amino esters, 177
hydrolysis by aqueous alkali, 183
polymerization, 193, 194
preparation, 125, *202*
reactions, with alcohols, 180
with aldehydes, 174
with amines, 180, 182
with aryl isocyanates, 191
with butynedioic acid, 171
with diamines, 180
with diphenylketene, 191
with nitrile oxides, 195
with trichloroacetic anhydride, 190
with water, 174, 182
reduction, 189
sodium derivative of, 153
toxicity of, 126
Ethoxyethynylcarbinols, 187
conversions, to amino esters, 178

to indenes, 177
to α,β-unsaturated aldehydes, 167
perhydrogenation, 189
pyrolytic decomposition, 197
reactions, with aldehydes, 176
with amines, 182
with thiobenzoic acid, 189
toxicity of, 126
Ethoxyethynyllithium, 158
Ethoxyethynylmagnesium bromide, condensation with ketones, 158
Ethoxyethynylsodium, 153
from chloroacetal, 154
from ethyl α,β-dibromoethyl ether, 154
1-Ethoxy-1-heptyne, 184
addition of alcohol to, 168
Ethoxypropyne, 193
Ethoxypropynoic acid, 155
4-Ethoxy-2-quinoline, 191
Ethoxyvinylcarbinols, 161
forced rearrangement, 163
Ethoxyvinyl ethers, 169
Ethoxyvinyltrialkylammonium hydroxides, 182
Ethyl acetoacetate, *C*-acylation with ketene, 233
reaction with isopropenyl acetate, 234
Ethyl allenyl ether, 124
Ethyl α-bromoacetoacetate, from diketene, 253
Ethyl butane-1,2,3,4-tetracarboxylate, 171
Ethyl carbonate, reaction with alkenylmagnesium halides, 28
Ethyl β-chlorocrotonate, nuclear magnetic resonance spectrum of, 320
Ethyl β-chlorovinyl ether, 125, *202*
reaction with hydroxylic compounds, 165
Ethyl cyclohexylideneacetate, preparation, *204*
Ethyl α,α-dichloroethyl ether, as reagent for acid chloride formation, 166
Ethylene-1,2-bisthioethers, conversion to ethynyl thioethers, 143
Ethylenic protons, and chemical shifts 282
N-Ethylethyleneimine, 312
Ethyl formate, reaction with alkenylmagnesium halides, 26
Ethyl orthoacetate, 168, 183
Ethyl orthoformate, 17
Ethyl orthothioacetate, 185
Ethylsulfenyl chloride, reaction with ketene, 220
(Ethylthio)acetaldehyde, 188
1-Ethylthio-2-alkoxy ethers, 184
1-Ethylthio-2-alkylaminoethenes, 184
1-Ethylthio-2-ethoxyvinylcarbinols, rearrangement, 187
(Ethylthio)ethyne, additions to, of hydrogen chloride, 165
of thio acids, 188
of thiolates, 185
hydration, 164
Mannich reaction with, 157
sodium derivative of, 154
(Ethylthio)ethynylcarbinols, 187
(Ethylthio)propyne, hydration, 164
(Ethylthio)propynoic acid, 155
Ethyl trichloroacetoacetate, 191
Ethyltrivinylgermane, preparation, 12
Ethynyl alkyl ethers, hydration to esters, 163
Ethynylcarbinols, conversion to α,β-unsaturated aldehydes, 201
Ethynylene bisthioethers, preparation and properties, 145–148
table of, 150
Ethynyl ethers, additions to, of halogens, 190
of thiols, 186
dielectric constants of, 140
infrared characteristics of, 149, 151
metallation, 153
preparation, 121
from acetals of chloroacetaldehyde, 122
from β-halogeno α,β-unsaturated ethers, 121

Ethynyl ethers (*continued*)
properties of, 126, 127
tables of, 127, 128
reactivity of, outline, 151–152
substitution of the ethynyl hydrogen atom by halogens, 156
Ethynyl thioethers, additions to, of alcohols, 184
of amines, 184
of halogens, 190
of thiols, 184, 186
behavior toward electrophilic reagents, 152
infrared characteristics of, 149, 151
mercury derivatives of, 153
metallation, 153
oxidative coupling, 156
preparation, 140
from ethylene 1,2-bisthioethers, 143
from β-halogeno α,β-unsaturated thioethers, 140
from sulfenyl halides, 143
properties of, 145
reactions involving the thioether group, 199
reactivity of, outline, 151
stability of, 145
Eucarvone, enol acetate of, nuclear magnetic resonance spectrum of, 317
External reference, 275

F

Field homogeneity, 271
First moment, 307
Flavanones, dehydrogenation, 341
Flavones, formation by dehydrogenation, 341
Fluorenone, irradiation, 374
Formamides, reaction with alkenylmagnesium halides, 30, 31
Formamidines, as hydrogen acceptor, 347
cis-β-Formylacrylic acid, 106
β-Formylpropionic acid, from 2-acetoxyfuran, 106
Friedel-Crafts reaction, with ketene, 233
with β-propiolactone, 239
Fulvene, formation from benzene, 407
Fumaric acid, photochemical conversion to maleic acid, 399
Furan, 111
Furans, electrolytic methoxylation, 71
from ethylthioethynyl compounds, 185
formation by dehydrogenation, 341
nuclear magnetic resonance spectra of, 314
Furfurylamine, 91, 94

G

Gelsemine, nuclear magnetic resonance spectrum of, 323
Geminal methylene coupling, 324
Geminal protons, coupling of, 309
Germanium, organic compounds of, 12
Germanium tetrachloride, 12
Gibberellic acid, nuclear magnetic resonance spectrum of, 319
Glucosaminic acid, 441
Glucose, conversion to glucuronic acid, 354
Glycols, monoethers of, 22
Glyoxaline, deuterium exchange in, 318
Grignard reagents, reactions, with ketene, 230
with, β-propiolactone, 239
Gyromagnetic ratio, 268

H

Haloalkanes, and nuclear magnetic resonance spectra, 285
Hamiltonian, 296
Hammett's constants, and chemical shifts, 278
correlation in dehydrogenation reactions, 332
Hantzsch ester, transfer hydrogenation with, 348
Hepta-2,5-diene-1-ol, 17
Heptindole, dehydrogenation, 339
Heteroannular dienes, irradiation, 406

Heterocyclic compounds, dehydrogenation, 339
Hexatrienes, formation by dehydrogenation, 338
cis-3-Hexene-2,5-dione, 80
n-Hexyltrimethylammonium iodide, 439
Hofmann degradation, of muscarine, 435
Homoannular dienes, irradiation, 403
  photochemical addition of oxygen, 403
Homoannular dienones, irradiation, 393
Homogeneous hydrogen transfer, 330
Hydrazoic acid, as reducing agent, 162
Hydrocarbazoles, dehydrogenation, 339
Hydrocortisone acetate, dehydrogenation, 344
Hydrogenation, 329 ff.
  homogeneous transfer, 348
Hydrogen bonding, effect in unshielding, 286
  and proton resonance, 280
Hydrogen cyanide, reaction with ketene, 222
Hydropolyacenes, dehydrogenation, 336
Hydroporphins, dehydrogenation, 340
Hydroxamic acids, from 2-acetylfuran, 95
m-Hydroxybenzoic acid, 98
α-Hydroxycarboxylic esters, reactions, with fumaric esters, 442
  with maleic esters, 442
1-(1′-Hydroxycyclohexyl)-2-ethoxyethyne, preparation, *203*
Hydroxyketenes, 197
Hydroxylation, of dihydrofurans, 73
cis-6-Hydroxy-7-methoxytropinone, 86
2-(Hydroxymethyl)-5-(aminomethyl)-furan, 92
6-Hydroxymethyl-3-pyridinol, 92
3-Hydroxy-2-piperidone, 94
6-Hydroxytropinone, 83
Hoyscine, 83

I

Imidazolines, 181
Imine *N*-oxides, formation by dehydrogenation, 341
Imines, β-lactams from, 198
Imino chlorides, reaction with alkenylmagnesium halides, 16
Indane, dehydrogenation, 337
Indanone, nuclear magnetic resonance spectrum of, 314
Indenes, preparation, 177
Indigo, isomerization, 400
Indirect coupling, 293
Indole, alkylation, 239
  nuclear magnetic resonance spectrum of, 314
  reaction with diketene, 249
Internal reference, 275
Iodoacetyl chloride, from ketene, 220
1-Iodo-2-ethoxyethyne, 156
trans-α-Ionone, photochemical isomerization, 392
trans-β-Ionone, 393
Ionones, synthesis, 338
β-Ionylideneacetaldehyde, synthesis, 120
Isatin, as hydrogen acceptor, 347
Isatogens, photochemical formation, 414
Isobutenyl bromide, reaction with lithium, 3
Isobutylene, nuclear magnetic resonance spectrum of, 307
Isodrin, irradiation, 392
Isophotosantonic lactone, 394
Isopropenyl acetate, acidolysis, 235
  preparation, 224
  reactions, with acids, 233, 235
    with alcohols, 233
    with aldehydes, 234
    with amines, 234
    with anhydrides, 235
    with halogens, 235
    with ketones, 234
Isopropyl alcohol, nuclear magnetic resonance spectrum of, 292

Isopropyl halides, α-protons in, 284
6-Isopropyl-3-pyridinol, 94
Isopyrocalciferol, 405
β-Isovalerolactone, 197

K

Ketals, from isopropenyl acetate, 233
Ketene, dimerization, 229
  enol acetates from, 224
  mercaptal, 185
  preparation, 214, 215
  reactions, with acid chlorides, 222
    with alcohols, 216
    with aldehydes, 225
    with amides, 219
    with amines, 218
    with amino acids, 218
    with aryl hydrazines, 218
    with carbonyl compounds, 226
    with carboxylic acids, 215
    with chlorine, 219
    with diazomethane, 230
    with enamines, 231
    with halogen compounds, 219
    with hydrogen cyanide, 222
    with hydroperoxides, 217
    with inorganic compounds, 229
    with organometallic compounds, 230
    with orthoformates, 223
    with phenols, 217
    with sulfur trioxide, 229
    with thiols, 217
    with α,β-unsaturated aldehydes, 227
    with α,β-unsaturated ketones, 227
    with water, 216
  toxicity of, 214
Ketols, from ethoxyethynylcarbinols, 187
Ketones (*see also* 1,4-Dicarbonyl compounds), α-acetylenic, 29
  cleavage products from, 382
  cyclic, photolysis, 372, 381
  dialkylamino, reaction with alkenylmagnesium halides, 25
  diazo, irradiation, 407
  α,α′-dihydroxy, 188
  enol acetylation, 234
  α′-halogeno, reaction with alkenylmagnesium halides, 23
  halogenoethylenic, reaction with alkenylmagnesium halides, 26
  irradiation, 372
  β-lactones from, 226
  photochemical hydrolytic cleavage, 382
  reactions, with alkenylmagnesium halides, 20
    with diketene, 254
  α,β-unsaturated, from alkoxydienes, 15, 16
    from diketene, 254
    enol acetates of, 224
    preparation, 29, 45, 57, 61
    reaction with ketene, 227
    rearrangement, 392
  from α,β-unsaturated alcohols, 20
Δ⁴-3-Ketosteroids, 1-dehydrogenation, 358
  photodimerization, 387
Kharasch addition, 379

L

β-Lactams, from ketene, 232
Lactones, from diketene, 243
  formation by dehydrogenation, 343
  hydrogenation, 240
  from keto esters, 227
  preparation, 226
  unsaturated, from diketene, 242
Lanostanone, photochemical hydrolytic cleavage, 382
Lattice, 269
Lead oxide, 111
Limonin, nuclear magnetic resonance spectrum of, 315
Linaloöl, synthesis, 21
Lindlar catalyst, 162
Line intensities, 300
Line width, in nuclear magnetic resonance spectra, 271
Lithium, organic compounds of, 2

Lithium aluminum hydride, 6, 162, 442
reduction of amides, 94
Lithium borohydride, 6
Longitudinal susceptibilities, 284
Lumiandrosterone, 382
Lumicolchicine, 398
Lumiprednisone acetate, formation, 398
Lumisantonin, 394, 395, 397
Lumisterol, 404
2,6-Lutidine, nuclear magnetic resonance spectrum of, 303

M

Magnesium bromide, 176
Magnetic anisotropy, 281
Maleic acid, photochemical interconversion with fumaric acid, 399
Mannich bases, reaction with alkenylmagnesium halides, 25
Mannich reactions, 157
Matrix elements, 299
Mercaptans, *see* Thiols
Mercury, organic compounds of, 13
Mercury spectrum, lines of, 369, 370
Metallic derivatives of ethynyl compounds, use in syntheses, 153
Methine protons, and chemical shift, 289
3-Methoxycyclohexane α-oxide, nuclear magnetic resonance spectrum of, 322
β-Methoxyethylmercury(II) acetate, nuclear magnetic resonance spectrum of, 321
2-Methoxyfuran, 102
5-Methoxy-2-methylfuran, 103
Methoxypropyne, 193
6-Methyl-6-acetoxycyclohexa-2,4-dione, irradiation, *415*
Methyl chlorovinyl ketone, reaction with alkenylmagnesium halides, 26
3-Methylcyclohexenone, photodimerization, 387
Methyldehydroursolate acetate, 405
2-Methyl-,4*5*-dicarbethoxytetrahydrofuran-3-one, 442
Methylene group, coupling within, 309
stereochemical effects, 309
Methyleneimine, as hydrogen acceptor, 347
Methylene protons, chemical shift of, 287
2-Methylene-1,3,3-trimethylindoline, reaction with ketene, 232
trans-β-Methylglutaconic acid, nuclear magnetic resonance spectrum of, 319
N-Methylglutarimide, reaction with vinylmagnesium bromide, 34
Methylheptenone, via diketene, 246
Methyl mercaptan, nuclear magnetic resonance spectrum of, 307
1-Methyl-3-methylenecyclobutene, nuclear magnetic resonance spectrum of, 321
β-Methylmuconic acid, nuclear magnetic resonance spectrum of, 320
9-Methyloctalin, dehydrogenation, 338
2-Methyloxazoline, reaction with ketene, 231
1-Methyl-1-phenyltetralin, dehydrogenation, 353
2-Methyl-3-pyridinol, 92
6-Methyl-3-pyridinol, 100
Methyl radicals, 372
2-Methyltetrahydrofuran, as solvent, 5
2-Methylthiazoline, reaction with ketene, 231
6-Methyl-2-thiouracil, reaction with diketene, 250
Monoalkenylboric acids, preparation, 13
Monoarylvinyl halides, reaction with magnesium, 1
Multiplet, 295
Multiplet moment theorems, 307
Muscarine, synthesis, 440
Muscarine chloride, 429, 432, 434
Muscarine iodide, 434
Muscarine Reineckate, 429, 434
Muscarine tetrachloroaurates, 428, 429, 434

Muscarine tetraphenylborate, 434
Muscarone, 438

N

Naphthalene, nuclear magnetic resonance spectrum of, 307
α-Naphthyl phenyl ketone, irradiation, 374
Neopentylvinyltins, preparation, 11
Neoprednisone acetate, formation, 398
Nerolidol, synthesis, 21
Nitric acid, reaction with ketene, 230
Nitriles, reaction with alkenylmagnesium halides, 35, 36
o-Nitrobenzaldehydes, photochemical conversion to o-nitrosobenzoic acid derivatives, 412
mechanism of, 413
Nitrobenzene, as acceptor in dehydrogenation reactions, 345
2-Nitro-4-chlorophenylsulfenyl chloride, reaction with ketene, 220
o-Nitrocinnamic acid, irradiation, 414
Nitrogen-nitrogen double bond, isomerization, 402
Nitrone-amide rearrangement, photochemically induced, 411
Nitroso radical, 375
o-Nitrostilbene, irradiation, 414
o-Nitrostilbene chloride, irradiation, 414
Nitrosyl chloride, irradiation, 375
reaction with ketene, 220
o-Nitrotoluenes, irradiation, 414
Nitryl chloride, reaction with ketene, 221
19-Nor-$\Delta^{5,7}$-Androstadiene-3β,17β-diol, 405
Normalization, of wave function, 298
Normuscarine, 436
19-Nortachysterol, 405
Nuclear magnetic moment, 268
Nuclear magnetic resonance, 265 ff.
Nucleophilic reagents, additions to the triple bond, 179
Nucleophilic substitution, of quinones, 334

O

Olefinic proton resonance, 285, 289, 290
Olefinic protons, and chemical shift, 288
Olefins, photochemical addition of aldehydes to, 377
reaction with ketene, 231
Organometallics, nuclear magnetic resonance spectra of, 321
reaction with ketene, 230
Organotin esters, 11
Organotin halides, 11
Orthogonality, 298
1,3-Oxazines, 250
Oxazirane, photochemical formation, 412
Oxazoles, photochemical formation, 385
Oxazolidines, 181
reaction with alkenylmagnesium halides, 19
Oxetanes, structure proof of, 380
Oxidation-reduction potential, of quinones, 331
Oxides, unsaturated, 23
2-Oxo-5-acetoxy-2,5-dihydrofuran, 106
2-Oxo-5-bromo-2,5-dihydrofuran, 106
2-Oxo-5-chloro-2,5-dihydrofuran, from 2-acetoxyfuran, 106
6-Oxo-1,3-dioxene-4 derivatives, 254
4-Oxoquinalidine, formation by dehydrogenation, 354
Oxygen transfer reactions, photochemically induced, 411

P

Palladium, in transfer hydrogenation, 350
Penicillin, 174
2-Pentanone-1,1,1,3,3-d_5, 372
Pent-2-en-4-one, preparation, *40*
Peptides, preparation via alkoxyethynes, 172
mechanism of, 173
Phenanthraquinone, in dehydrogenation, 336
Phenanthraquinone imide, 385
Phenanthrene, photochemical formation from stilbene, 401

Phenol, from irradiation of prednisone acetate, 398
Phenols, reactions, with diketene, 243
with β-propiolactone, 237
Phenoxyethyne, 118, 198
hydration, 164
metallic derivatives of, 190
polymerization, 193
sodium derivatives of, 153
1-Phenoxy-1,2,2-triiodoethene, 190
m-Phenylbenzophenone, irradiation, 374
Phenyldiazomethane, derivatives of, decomposition, 410
1-Phenyl-2-ethoxy-4-hydroxynaphthalene, 191
Phenylethyne, 192, 193
Phenylglyoxylic acid, irradiation, 374
Phenylhydrazine, reaction with diketene, 249
Phenyl isocyanate, reaction with alkenylmagnesium halides, 35
1-Phenyl-2-methoxyethyne, polymerization, 193
1-Phenylnaphthalene-2,3-dicarboxylic anhydride, 171
Phenylpropiolic acid, 171
2-Phenylthiophene, formation by dehydrogenation, 342
Phosphoric acid, reaction with ketene, 230
Photochemical dimerization, 387
Photochemical hydrogen transfer, 355
Photochemical additions of aldehydes, 383, 386, 387
to acetylenes, 380
to olefins, 377
to quinone imides, 385
Photochemical rearrangement, of azoxybenzene, 412
Photochemical transformations, 367 ff.
Photosantonic acid, 394
nuclear magnetic resonance spectrum of, 323
Phthalimidines, reaction with diketene, 249
Phytol, 248
Pinacones, by irradiation of carbonyl compounds, 373
β-Pinene epoxide, 18
Point dipole approximation, 283
Polyacenes, 334
Polyenes, 17
cyclic, irradiation, 403
Polymerization, 193
of alkenylborates, 13
of β-lactones, 237
photochemically induced, 414
Potassium borohydride, as reducing agent, 448
Precalciferol, 404
Prednisone, from cortisone, 358
Prednisone acetate, irradiation, 395
Propane, nuclear magnetic resonance spectrum of, 307
Propargyl bromide, reaction with vinylmagnesium bromide, 17
Propargyl ethers, 125
Propargylic alcohols, dehydrogenation, 342
Propene, metallation, 2
cis-Propenyl bromide, reaction with lithium, 2
β-Propiolactone, formation by irradition of diazoketones, 408
polymerization, 236
reactions, 237–239
Propoxyethyne, reaction with hydrogen chloride, 172
Proton exchange, 312
Proton resonance, in aldehydes, 280
in aromatic systems, 280
in chelates, 280
and hydrogen bonding, 280
in *C*-methyl groups, 280
in olefinic groupings, 280
Protons, and chemical shifts, 282, 287, 288, 289, 292
coupling of, 309
magnetically equivalent, 302
and nuclear magnetic resonance spectra, 285, 314
residence times of, 312
Proton system, AB, 296, 301

Proton system (*continued*)
AB_2, 302
AB_3, 307
A_2B, 296
A_2B_2, 305
A_2B_6, 307
ABC, 304
ABX, 304
AB_2X_2, 307
AX, 294
AX_2, 302
A_2X, 294
A_2X_2, 305
Pseudoirone, synthesis via diketene, 248
Purpurogallin, rearrangement, 399
Pyran derivative from ionone, 393
Pyridazines, from 1,4-dicarbonyl compounds, 81, 83
Pyridine, nuclear magnetic resonance spectrum of, 307
2,3-Pyridinediol, from 2-carbomethoxyfuran, 94
3-Pyridinols, from dihydrofurans, 90, 99
Pyridoxine, synthesis, 93
Pyrimidones, from diketene, 250
Pyrocalciferol, 405
Pyrolysis, of acetoacetates, 244
of ethynylcarbinyl acetoacetates, 247
of β-lactone polymers, 236
α-Pyrone, irradiation, 394
Pyrrole, alkylation, 239
Pyrroles, from 2,5-dimethoxytetrahydrofurans, 101
from furans, 100
reaction with diketene, 249

Q

o-Quinonediazide, photolysis, 408
Quinone imides, photochemical additions of aldehydes, 385
Quinones, dehydrogenation reaction, mechanism of, 331
oxidation-reduction potential of, 333
as oxidizing agents, 331
photochemical addition reactions, 383, 384

R

Radicals, acetyl, 372
allylic, 375
generation of in photolysis, 372
Rearrangement, of azoxybenzene to *o*-hydroxyazobenzene, 412
of ethoxyethynylcarbinols, 182
of ethoxyvinylcarbinols, 163
of isopropenyl acetate, 235
of nitrones to amides, 411
of unsaturated alcohols, 26
Reduction, of dihydrofuranones, 448, 449
of ethoxyethynylcarbinols, 162
partial, of triple bond, 162
Reference compound, in nuclear magnetic resonance spectra, 275
Regular solution, in nuclear magnetic resonance spectra, 276
Reineckate, of muscarine, 429, 434
Residence times, of proton, 312
Resolution, of *d,l*-muscarine chloride, 453
Ring closure, 185
Ring current, 282
Ring size, and ease of dehydrogenation, 337
Robinson-Schöpf reaction, 81
Rotational barrier, and nuclear magnetic resonance spectra, 313

S

Santonin, photochemistry of, 394–395
Saturation (factor), 270
Schiff's bases, reactions, with alkenylmagnesium halides, 37
with ketene, 231
Schrödinger equation, 296
Scopine, 83
Scopolamine, 83
Scopoline, synthesis, 86
Second moment, 308
Secular determinant, 299
Secular equation, 298

Shielding, of methyl derivatives, 280
Shielding constants, 273
  of molecular hydrogen, 274
  of protons of water, 274
  standardization of, 274
Sideband technique, 274
Silicon, organic compounds of, 10
Sodamide, dehydrohalogenation with, 126
Sodium, organic compounds of, 2
Solvent, role in formation of organometallics, 6
Sorbic acid, preparation from ketene, 228, 237
Spin angular momentum, 296
Spin-coupling, mechanism of, 291
Spin-lattice relaxation, 269
Spin operators, 299
Spin orientations, 294
Spin-spin multiplets, 273
Spin temperature, 269
Spin wave function, 297
Spirilloxanthin, nuclear magnetic resonance spectrum of, 323
Sterculic acid, nuclear magnetic resonance spectrum of, 316
Steroid, nuclear magnetic resonance spectra of, 314
trans-Stilbene, isomerization, 400
  preparation, 338
Styrene, vinyl grouping in, and nuclear magnetic resonance spectrum, 304
β-Styrylmagnesium bromide, preparation, 2
Succinaldehyde, 80, 89
Sulfoacetic anhydride, from ketene, 229
Sulfonamides, reaction with diketene, 249
Sulfonic acids, conversion to anhydrides, 170
Sulfur dichloride, reaction with ketene, 220
Sulfur dioxide, photochemical addition to *o*-quinones, 383
Sulfuric acid, reaction with ketene, 229
Sulfur monochloride, reaction with ketene, 220
Sulfuryl chloride, reaction with ketene, 220
Suprasterol-II, 406

T

Tachysterol, 404
Teloidinone, 86
Terebic acid, photochemical synthesis, 381
Terreic acid, nuclear magnetic resonance spectrum of, 316
Tetrachloro-1,2-benzoquinone, 333–335
  preparation, *359*
Tetrachloro-1,4-benzoquinone, *see* Chloranil
3,3′,5,5′-Tetrachloro-4,4′-diphenoquinone, 333, 336, *361*
Tetracyanoethylene, 334
  adduct with 1,2-diphenyl-3,4-dimethylenecyclobutene, nuclear magnetic resonance spectrum of, 315
Tetraethyl pyrophosphate, 171
Tetrahydrocarbazole, dehydrogenation, 339, 354
Tetrahydrofuran, as solvent in preparation of alkenylmagnesium halides, 3
Tetrahydrofuranones, 442
Tetrahydrofurans, from 1,4-diols, 144
Tetrahydroharmane, dehydrogenation, 354
Tetrahydro-β-ionylideneacetaldehyde, 119
1,2,3,4-Tetrahydroisoquinoline, dehydrogenation, 340
Tetrahydrometoxazines, reaction with alkenylmagnesium halides, 19
Tetrahydronaphthalenes, dehydrogenation, 337
Tetrahydropyran, as solvent, 5
Tetralin, dehydrogenation, 337
α-Tetralone, irradiation, 374
2,3,4,5-Tetramethoxytetrahydrofuran, 87
Tetramethyltin, as dehydrogenation promotor, 353

Tetranitromethane, from ketene, 230
Tetraphenylcyclobutane, photochemical formation from stilbene, 401
2,3,4,5-Tetraphenylcyclopentadienone, reaction with isopropenyl acetate, 236
2,3,4,5-Tetraphenyl-6-methylbenzene, 236
Tetravinyltins, preparation, 11
Thiazolidines, 181
Thioethers, β-halogeno, α, β-unsaturated, elimination of hydrogen halide, 140
preparation, 141
Thioindigo, isomerization, 400
Thiolates, addition to ethylthioethyne, 185
Thiol esters, 161
α,β-unsaturated, from ethynyl ethers, 176
Thiols, reactions, with diketene, 251
with β-propiolactone, 237
Thionyl chloride, reaction with ketene, 220
Thiophene, as dehydrogenation promotor, 353
Thiophenes, formation by dehydrogenation, 342
Thiourea, reaction with diketene, 250
Thujane, photochemical synthesis, 410
Thymoquinone, photodimerization, 387
Tiglic acid, isomerization, 400
Tin, organic compounds of, 11
Transfer hydrogenation, 351
of polynitro compounds, 352
Transition probability, 269
Transverse susceptibilities, 284
2,3,5-Trialkoxytetrahydrofurans, preparation, 78, 79
Trichloroacetic anhydride, 171
Trichloromethylvinylcarbinols, from chloral, 24
Trienes, from unsaturated alcohols, 26
1,2,2-Tri(ethylthio)ethane, 186
2,3,6-Trimethoxybenzoic acid, from methyl fuorate, 97
2,3,5-Trimethoxy-4-hydroxytetrahydrofuran, 87
2,5,5-Trimethoxytetrahydropyran, synthesis, 102
1,3,3-Trimethylcyclohexylhydroperoxide *p*-nitrobenzenesulfonate, nuclear magnetic resonance spectrum of, 321
Trimethylene oxide, photochemical formation, 379
1,1,2-Triphenylethane, dehydrogenation, 338
Triphenylmethyl chloride, reaction with ketene, 221
Triple bond, addition of thiols, 185
free radical additions to, 186
partial reduction, 162
Triplet state, 372
Triterpenes, irradiation, 405
Trivinylarsine, 12
Trivinylstibine, 12
Tropenone, 85
Tropinone, 81, 82
preparation, *110*
Tropolones, from furans, 98
irradiation, 398
α-Truxillic acid, 389
β-Truxinic acid, 389

U

Uncertainty broadening, of line width, 271
2,4,6-Undecatrien-8-one, preparation, 34
α,β-Unsaturated compounds, *see* Acids; Alcohols; Aldehydes; Carbonyl compounds; Esters; Ketones
Urea, reaction with diketene, 250

V

Variation method, 298
Vicinal coupling, 324
Vicinal protons, coupling of, 309
Vinylacetic anhydride, preparation, *206*
Vinylation agent, 13

Vinyl function, and nuclear magnetic resonance spectrum, 323
Vinylgermanes, preparation, 12, 42
Vinyl halides (*see also* individual halides), 1
Vinylidene chloride, conversion to *cis*-bis(*p*-tolythio)ethene, 144
Vinylmagnesium halides, preparation, *37, 38*
Vinylmercury halides, preparation, 11
3-Vinyl-2-methylcyclohex-2-enone, preparation, *39*
Vinylsilanes, preparation, 10, 41
Vinylsodium, 2
Vinyltin chlorides, preparation, 11
Vinyltins, preparation, 10, 41
Vinyl(tri-*n*-butyl)tin, preparation, *38*
Vitamin A, 248
  polyene ketone related to, 200
Vitamin A acid, 338
Vitamin A aldehyde, synthesis, 120
Vitamin D, formation, 403
Volume diamagnetic susceptibility, 275

W

Wave function, 297

X

Xanthone, irradiation, 374

Advances in Organic Chemistry: Methods and Results

CUMULATIVE INDEX, VOLUMES I–II

	VOL.	PAGE
Alkenylmagnesium Halides (Normant)	II	1
Dialkoxydihydrofurans and Diacyloxydihydrofurans as Synthetic Intermediates (Elming)	II	67
Ethynyl Ethers and Thioethers as Synthetic Intermediates (Arens)	II	117
Hydrogenation-Dehydrogenation Reactions (Jackman)	II	329
Hydroxylation Methods (Gunstone)	I	103
Ketene in Organic Synthesis (Lacey)	II	213
Kolbe Electrolytic Synthesis (Weedon)	I	1
Muscarine (Eugster)	II	427
Nuclear Magnetic Resonance in Organic Structural Elucidation (Conroy)	II	265
Optical Rotatory Dispersion and the Study of Organic Structures (Klyne)	I	239
Polyphosphoric Acid as a Reagent in Organic Chemistry (Uhlig and Snyder)	I	35
Selective Degradation of Proteins (Thompson)	I	149
Ultraviolet Photochemistry of Simple Unsaturated Systems (Mayo)	II	367
Wittig Reaction (Trippett)	I	83

PRINCIPAL.
REGIONAL TECHNICAL COLLEGE,
PORT ROAD,
LETTERKENNY.

PRINCIPAL,
REGIONAL TECHNICAL COLLEGE,
PORT ROAD,
LETTERKENNY

70884